PROTOCOL: 1042-PPD-2003

TITLE: **A Phase 2, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of IV and Oral Administration of Ganaxolone in Women with Postpartum Depression**

DRUG: Ganaxolone (CCD 1042:3α-hydroxy-3β-methyl-5α-pregnan-20-one)

IND: 135256

SPONSOR:

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PROTOCOL SIGNATURE PAGE

Sponsor's (Marinus) Approval

Signature: RGutierrez MD	**Date:** 23 OCT 2018
Rolando Gutierrez-Esteinou, MD Vice President, Clinical Development and Pharmacovigilance	

Investigator's Acknowledgement

I have read this protocol for Marinus Study 1042-PPD-2003.

Title: A Phase 2, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of IV and Oral Administration of Ganaxolone in Women with Postpartum Depression

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____ _____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-24}	area under the concentration curve
β-HCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C_{max}	maximum plasma concentration
C_{min}	Minimum plasma concentration
CNS	central nervous system
CRA	clinical research associate
CRC	child-resistant closure
CRO	contract research organization
Css	concentration at steady-state
CSSRS	Columbia Suicide Severity Rating Scale
CTNI	Clinical Trial Network Institute of Massachusetts General Hospital
CYP	Cytochrome P
DBPC	Double-blind placebo-controlled
DRC	Data Review Committee
EC	Ethics Committee
ECG	electrocardiogram
ECT	Electroconvulsive Therapy
eCRF	electronic case report form
EMA	European Medicines Agency
EPDS	Edinburgh Postnatal Depression Scale
EU	European Union
FDA	Food and Drug Administration
GABA	gamma Aminobutyric Acid
GCP	Good Clinical Practice
GCMS	gas chromatography mass spectroscopy
GMP	Good Manufacturing Practices

HAMD	Hamilton Depression Rating Scale
hCG	human chorionic gonadotropin
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IP	Investigational product
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MINI 7.0	Mini International Neuropsychiatric Interview 7.0
mITT	modified Intent to Treat
OL	open-label
PCDH19	protocadherin 19
PD	pharmacodynamic
PK	pharmacokinetic
PPD	postpartum depression
PTSD	Post-traumatic stress disorder
QID	4 times daily
Q4H	every 4 hours
QHS	nightly at bedtime
QTcF	QT interval Fridericia's correction
rTMS	rapid transcranial magnetic stimulation
SAE	serious adverse event
SAFER	State versus trait; Assessability; Face validity; Ecological Validity; and Rule of 3 Ps
SAP	statistical analysis plan
SOP	standard operating procedure
SSRIs	selective serotonin reuptake inhibitors
SSS	Stanford Sleepiness Scale
STAI	Spielberger State-Trait Anxiety Inventory
TEAE	Treatment Emergent AEs
TID	3 times daily
TSH	thyroid stimulating hormone

ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number:	**Drug:**
1042-PPD-2003	Ganaxolone IV, oral suspension, and oral capsule formulations

Title of the study: A Phase 2, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of IV and Oral Administration of Ganaxolone in Women with Postpartum Depression

Design:

This is a Phase 2, multicenter study in women with postpartum depression (PPD) consisting of 2 parts: An Open Label Part with multiple ascending doses focused on safety and tolerability in 5 groups that differ by total daily dosing and formulation of study drug; and a Double-blind Placebo-controlled (DBPC) part focused on safety, tolerability and efficacy in one group. The DBPC Part will begin after the Open Label Part dosing is completed. The dosing, treatment duration and timing of evaluations for the double-blind portion of the study will be decided based on the results of the Open Label Part and recommendations of the Data Review Committee (DRC). The DRC is comprised of Marinus' Chief Medical Officer and 2 external physician experts.

Figure 1-A and Figure 1-B depict the design for each subject group in the Open Label and DBPC Parts, respectively.

Number of subjects and dose regimen for each treatment arm:

For the Open Label Part, approximately 176 women aged 18 to 48 years with PPD will be screened to enroll approximately 88 subjects.

The first group (called open-label 3 times daily [OL TID]) of approximately 8 subjects will receive oral ganaxolone (capsules) titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days.

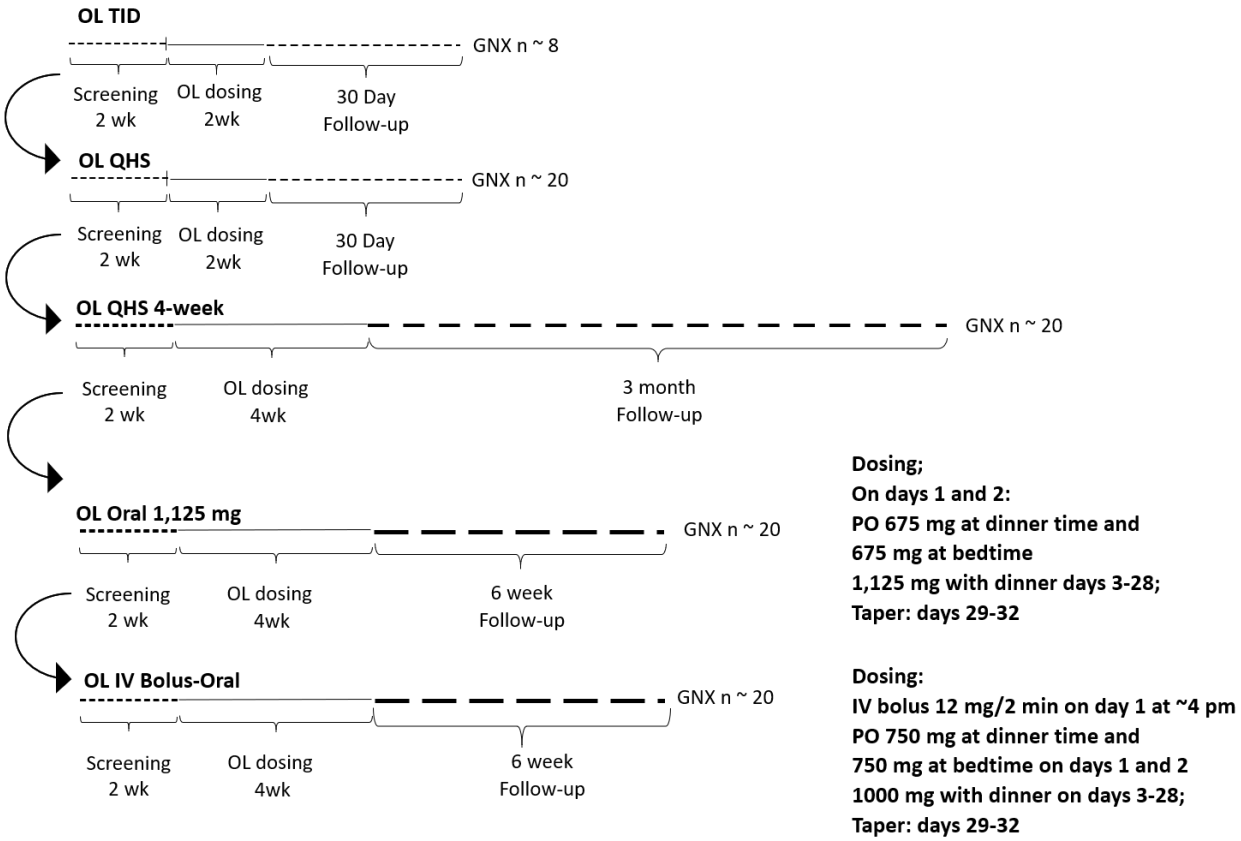
The second group (called open-label administered at bedtime [OL QHS]) of approximately 20 subjects will receive oral ganaxolone (capsules) at bedtime (QHS), titrated to a dose of 675 mg QHS over 4 days and maintained until Day 10, followed by a taper over 4 days.

The third group (called OL QHS 4-week) of approximately 20 subjects will be administered oral ganaxolone (capsules) at a dose of 675 mg QHS for 28 days, followed by a taper over 4 days.

The fourth group (called OL 1,125 mg group) of approximately 20 subjects will receive on the first 2 days, oral ganaxolone capsules at a dose of 675 mg at approximately 7 pm (with dinner) and 675 mg at 10 pm (with a fatty snack), followed by 26 days of ganaxolone 1,125 mg at dinner time, and a taper over 4 days. Approximately 6 subjects will participate in pharmacokinetics (PK) collection that requires an overnight stay on Day 1.

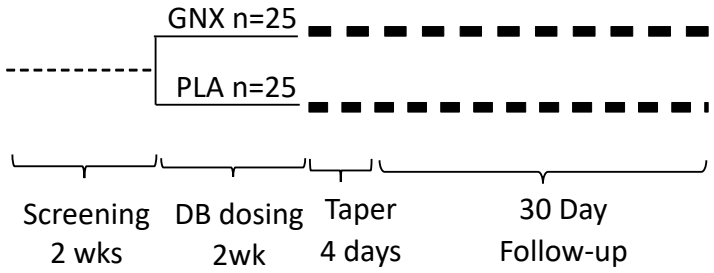
The fifth group (called OL Bolus-oral) of approximately 20 subjects will receive ganaxolone starting with a single intravenous (IV) 12 mg bolus over 2 minutes at approximately 4 pm of Day 1, followed by ganaxolone oral suspension 750 mg at 6pm (with a fatty meal), and 750 mg at 10pm (with a fatty snack). On Day 2, subjects will receive ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime, followed by 26 days of ganaxolone oral suspension 1,000 mg at dinner time. Treatment will then be tapered over 4 days. Approximately 6 subjects will participate in PK collection that requires an overnight stay on Day 1.

Figure 1-A: Design of Open-Label Part



For DBPC part, approximately 100 women with PPD aged 18 to 48 years will be screened to randomize 50 women in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days. The dosing, treatment duration and timing of evaluations for the double-blind portion of the study will be decided based on the results of the Open Label Part and recommendations of the DRC. The total daily dose will not exceed 1,600 mg. Randomization will be stratified by the use of concomitant antidepressants so that the number of subjects who are treated with antidepressants and who are not treated with antidepressants will be similar in each treatment group.

Figure 1-B: Design of the Double-Blind Placebo-Controlled Part



The investigator has the flexibility to adjust the dose and/or timing of the dose if the subject experiences sedation, dizziness or other untoward effects in each dosing group, by reducing the dose first to a lower level and possibly increasing it later if tolerance develops to the untoward effects (see Section 6.2.7).

Site(s) and Region(s): Approximately 30 investigational sites in the United States

Study period (planned): September 2017 to June 2019	**Clinical phase:** Phase 2

Objectives:

Open-Label Part: Safety, dosing, efficacy and pharmacokinetics

1. To assess the safety and tolerability of ganaxolone in women with PPD as determined by adverse events (AEs), changes from baseline in laboratory measures, vital signs, Columbia Suicide Severity Rating Scale (CSSRS), electrocardiogram (ECG), Stanford Sleepiness Scale (SSS), and physical examination.
2. To develop an optimal dosing regimen for the double-blind part. Adverse events and other safety data, including sedation and dosing changes will be adjudicated by the DRC before proceeding to the double-blind part of the study.
3. To assess the efficacy of ganaxolone using the Hamilton Depression Rating Scale 17-item version (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory 6-item version (STAI6) and Clinical Global Impression-Severity and Improvement (CGI-S and CGI-I) scales.
4. To collect samples of blood for PK analysis after administration of oral and IV ganaxolone to use in population-PK analyses, the results of which will be reported separately by the Sponsor.

Double-Blind placebo controlled (DBPC) Part: Safety, efficacy, and pharmacokinetics

Safety objective: To assess the safety and tolerability of ganaxolone vs placebo in women with PPD as determined by AEs and changes from baseline in laboratory measures, vital signs, CSSRS, ECG, SSS, and physical examination.

Efficacy objective: To assess the efficacy of ganaxolone vs placebo using the HAMD17, EPDS, STAI6 and CGI-S and CGI-I scales.

The primary efficacy variable in this study is change from baseline in the HAMD17 total score on Day 10 of the DBPC part between ganaxolone and matching placebo.

Pharmacokinetic objective: To collect samples of blood for PK analyses after administration of oral ganaxolone to use in population-PK analyses, the results of which will be reported separately by the Sponsor.

Rationale: Rapidly declining plasma levels of allopregnanolone and other neurosteroids after childbirth are thought to be linked to triggering depression in women who are vulnerable to develop this condition. Ganaxolone, a synthetic analog of allopregnanolone, may provide benefit to these women. This study is intended to test the safety and efficacy of ganaxolone in the treatment of PPD.

Investigational product, dose, and mode of administration: Ganaxolone IV, oral suspension, and oral capsule (225 mg/capsule) formulations and matching placebo will be used.

Inclusion Criteria:

1. An understanding of and ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
3. Female aged 18 to 48 years inclusive, at the Screening Visit
4. Experiencing a major depressive episode, which started between the start of the third trimester and 4 weeks following delivery. The major depressive episode must be diagnosed according to Mini International Neuropsychiatric Interview (MINI) 7.0 interview
5. Given birth in the last 12 months
6. HAMD17 score of ≥ 20 at screening rated by a certified site rater.

7. HAMD17 ≥ 18 (rated by CTNI) on Day 1 prior to study drug administration
8. The diagnosis of PPD and severity of depression must be supported by the State versus trait; Assessability; Face validity; Ecological Validity; and Rule of 3 Ps (SAFER) interview
9. Must agree to stop breastfeeding from start of study treatment until 45 days after receiving the last dose of the study drug
10. Must agree to use acceptable contraceptive methods during the study period
11. Must have a reliable family member, significant other or a trusted friend who can take a role as the primary childcare provider and support person at home (including during the night) while the subject is participating in the trial

Exclusion Criteria

1. Current or past history of any psychotic illness, including major depressive episode with psychotic features
2. Any psychiatric condition that, in the investigator's judgment, is considered clinically significant and could affect subject safety or study outcome including eating disorder, panic disorder, obsessive-compulsive disorder, or post-traumatic stress disorder
3. History of suicide attempt within the past 3 years
4. Active suicidal ideation (e.g., answering "yes" to questions 4 or 5 in the CSSRS suicidal ideation section)
5. History of severe bipolar I disorder (e.g. hospitalization due to the illness, lifetime history of psychosis or suicide attempt).
6. Uncontrolled seizure disorder
7. Current or history within the past 3 years of alcohol or any substance use disorder, with the exception of tobacco or caffeine
8. Positive drug screen for any illicit substances or prescription drugs at screening or randomization. If the drug screen is positive for a prescription drug that has the potential to be abused (e.g., amphetamine, benzodiazepine), legitimate use of the drug must be verified by the subject's providing the current pill bottle, prescription for the drug, or a note from the prescribing physician. Cannabis use is prohibited, and subjects with positive drug screen for cannabis are excluded. However, occasional users of cannabis may be re-tested after 5 days if the subject is willing to refrain from consuming cannabis-based products during the trial. If the re-test sample is negative at screening, the subject can be considered eligible. If the re-test sample is positive for cannabis, the investigator may ask for determination of blood levels of Δ9-tetrahydrocannabinol (THC), and its metabolites 11-hydroxy-THC and 9-carboxy-THC. If THC is not detectable, the subject is eligible for the trial.
9. Current or relevant history of any medical disorder that may require treatment or make the subject unlikely to be able to complete the study, or any condition that presents undue risk from the investigational product or procedure point of view
10. Any clinically significant abnormality identified on physical examination, ECG, or laboratory tests that in the judgment of the investigator would compromise the subject's safety or successful participation in the clinical study
11. Subject has untreated or uncontrolled hypothyroidism
12. Known or suspected intolerance or hypersensitivity to the investigational product(s) or allopregnanolone, or any of the stated ingredients
13. Use of another investigational product within 60 days prior to the first dose of investigational product
14. Has alanine transferase (ALT) or aspartate transferase (AST) greater than 2.5 times upper limit of normal or total bilirubin greater than 1.5 times upper limit of normal (unless elevation is due to Gilbert's syndrome)
15. Screening QT interval Fridericia's correction (QTcF) > 470 msec
16. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or concentrated citrus derived products from diet between screening and last on-treatment visit
17. Receiving concomitant treatment with strong cytochrome P (CYP)3A4 inducers or strong CYP3A4 inhibitors
18. Body mass index (BMI) ≥ 40

19. Subject is pregnant
20. Subject is using prohibited medications as specified in Section 5.3.2

Maximum duration of subject involvement in the study: Approximately 7 weeks for the OL TID and OL QHS groups and the DBPC part. The duration for the OL QHS 4-week group is approximately 18 weeks and the duration for the OL 1,125 mg and OL Bolus-oral groups is approximately 12 weeks.

Key variables:

Safety: Adverse events, laboratory measures, vital signs, CSSRS, ECG, SSS, and physical examination.

Efficacy: HAMD17, EPDS, STAI6, CGI-I and CGI-S scales.

Pharmacokinetics: For the OL TID and OL QHS groups, a total of 5 samples of blood will be collected to determine ganaxolone plasma concentrations during the study. Samples will be collected on 3 occasions during treatment with ganaxolone to determine trough concentrations in plasma. An additional 2 samples of blood will be collected at follow up visits, after ganaxolone treatment has been completed, to monitor the disappearance of ganaxolone following cessation of treatment. For the OL QHS 4-week, OL 1,125 mg, and OL Bolus-oral groups, 6 samples of blood will be collected to determine ganaxolone plasma concentrations during the study. Samples will be collected on 4 occasions during treatment in the OL QHS 4 weeks group and on 5 occasions during treatment in the OL 1,125 mg and OL Bolus-oral groups to determine ganaxolone trough concentrations in plasma. Two additional samples of blood will be collected in the first 2 follow up visits in the OL QHS 4 weeks group and 1 additional sample will be collected in the OL 1,125 mg, and OL Bolus-oral groups at the first follow up visit after ganaxolone treatment has been completed, to monitor the disappearance of ganaxolone following cessation of treatment.

Statistical Methods: Data will be presented by study part (OL, DBPC), dosing or treatment group within study parts and if applicable, study visit. Continuous variables will be summarized as numbers of observations, means, measures of variance (e.g., standard deviation), and percentiles (e.g., median, minimum, maximum). Categorical variables will be summarized as numbers of observations and percentages.

Analysis Populations: The Screened Set will consist of all subjects who have signed an informed consent. The Randomized Set will consist of subjects randomized in the DBPC part of the trial. The Safety Set will consist of all subjects who received investigational product (IP). The modified Intent to Treat (mITT) Set will consist of all subjects in the DBPC part of the trial who received IP, and who have at least 1 post-baseline HAMD17 assessment. The Per-Protocol Set will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints.

Efficacy Analysis: Efficacy parameters will be summarized for both the OL and DBPC parts, but will be analyzed only for the DBPC part. The primary time point of interest for all efficacy parameters will be Day 10 for the DBPC part and the visit at end of treatment (before initiation of taper) for the OL part. The primary efficacy endpoint will be change from baseline in HAMD17 total score at Day 10 for the DBPC part and at the visit at end of treatment for the OL part. The primary efficacy analysis will be done using the mITT set (DBPC group only), and the analytical method will be mixed model repeated measures (MMRM) with baseline HAMD17 total score as a covariate. Significance will be tested at a two-sided 0.05 level.

Secondary efficacy endpoints will be change from baseline in HAMD17 total score other than at the primary endpoint time point, HAMD17 response defined as at least a 50% reduction from baseline in total score, HAMD17 remission defined as total score < = 7, change from baseline in EPDS total score, change from baseline in STAI6, and CGI-Improvement. HAMD17 and EPDS individual items as well as several HAMD17 subscales will be considered exploratory.

1 BACKGROUND INFORMATION

1.1 Postpartum Depression (PPD)

Postpartum depression (PPD) is a mood disorder that occurs in about 7% of women following the birth of a child.[1] Common symptoms include feelings of extreme sadness, hopelessness, suicidal ideation, anxiety, and fatigue, which mirror those of a major depressive episode with the additional criteria that the onset of depression occurs within 4 weeks of childbirth. PPD can affect a mother's ability to care for her child and may negatively affect a child's cognitive development.[2]

Rapid changes in the levels of endogenous neurosteroids during pregnancy are thought to be related to the development of PPD. Plasma levels of allopregnanolone, which is a metabolite of progesterone and an endogenous gamma-aminobutyric acid (GABA) receptor modulator, are known to increase throughout pregnancy and then precipitously drop after delivery.[3, 4] It is thought that these rapid hormonal changes are linked to triggering depression in women who are vulnerable to develop this condition. Serotonin selective reuptake inhibitors (SSRIs) are known to increase allopregnanolone, and it has been suggested that this mechanism could explain why SSRIs have shown therapeutic effect in the treatment of PPD.[5] There have been a limited number of placebo-controlled randomized clinical trials testing the efficacy of SSRIs, or any other medication, in the treatment of PPD.[6,5]

Data were recently published that demonstrated that a continuous infusion of allopregnanolone rapidly alleviates symptoms of depression in women with PPD.[7] In this open-label study, 4 women with severe PPD received a 60-hour infusion of allopregnanolone. The mean Hamilton Depression Rating Scale for Depression (HAMD) before the infusion was 26.5, indicating that the women were severely depressed. Mean HAMD total score showed robust reductions even at the earliest time point measured (Mean HAMD 4.8 at Hour 12) and remained substantially lower through the end of infusion (Mean HAMD 3.3 at Hour 24, 1.8 at Hour 36, 2.3 at Hour 48, and 1.8 at Hour 60). Other end points showed similar improvements.

1.2 Product Background and Clinical Information

Ganaxolone is the 3β-methylated synthetic analog of the progesterone metabolite allopregnanolone. Allopregnanolone exhibits potent anxiolytic, antidepressant, antiepileptic, and sedative activity by virtue of its $GABA_A$ receptor modulating properties. As with allopregnanolone, ganaxolone potentiation of the $GABA_A$ receptor occurs at a site distinct from the benzodiazepine site. However, unlike allopregnanolone, ganaxolone cannot be converted to a hormonally active steroid.[8] Ganaxolone has been studied in completed and ongoing clinical trials in healthy adults, adult subjects with epilepsy, adults with post-traumatic stress disorder (PTSD), adults with migraine, children with refractory epilepsy and seizure disorders including female pediatric subjects with protocadherin 19 (PCDH19) epilepsy, and children with Fragile X Syndrome.

1.2.1 Ganaxolone: Oral Administration

As of 28 Sep 2016, approximately 1,588 unique subjects have received treatment with ganaxolone oral formulations in ongoing and completed clinical trials ranging in duration from 1 day to more than 2 years, using doses from 50 to 2,000 mg/day. Of these, 1,148 unique subjects have received ganaxolone oral formulation in completed studies. In 19 completed Phase 1 studies, 289 healthy subjects received ganaxolone orally at doses of 50 to 2,000 mg/day for periods of up to 2 weeks. Ganaxolone when given at doses 1,000 mg BID to healthy volunteers resulted in average C_{max} and C_{min} concentrations of 262 ng/ml and 57 ng/ml.

In the 18 completed Phase 2 clinical studies, 859 unique subjects have received oral ganaxolone at doses up to 1,500 mg/day including 169 adult subjects with epilepsy, 135 pediatric subjects with seizure disorders, 59 pediatric subjects with Fragile X syndrome, 393 adult subjects with migraine, and 103 subjects with PTSD.

In clinical trials of ganaxolone, adverse events (AEs) related to the GABAergic mechanism of action such as dizziness, sedation and sedation-related AEs (fatigue, somnolence), ataxia and diplopia, were reported more commonly in subjects receiving ganaxolone than placebo. In general, the frequency of these events was dose related. Most of these effects were reported as mild or moderate in severity and were reversible after dose decrease or drug discontinuation.

In the largest clinical trial conducted so far, Study 1042-0603, a Phase 3 trial of ganaxolone in adults with drug-refractory partial onset seizures, the safety profile of ganaxolone was consistent with previously conducted studies. In the double-blind portion of this study, 359 subjects were randomized to receive oral ganaxolone (900 mg twice a day) or placebo for 14 weeks. Overall, ganaxolone was generally safe and well tolerated with no imbalance between the ganaxolone and placebo group in the number of subjects with serious adverse events (SAEs) (5% vs 5.1%). The most common AEs (> 5%) reported at greater rates than placebo were somnolence (23.5% vs 4.5%), dizziness (19.6% vs 4.5%), and fatigue (11.7% vs 6.8%). Most of these AEs were rated as mild in severity. There were 44 (25%) subjects treated with ganaxolone that discontinued the study compared with 26 (14%) subjects on placebo. The most common reason for discontinuation was AE. Nine subjects experienced SAEs in placebo and ganaxolone groups each.

In the ganaxolone development program overall, no clinically significant trends in electrocardiogram (ECG) intervals, vital signs, or physical or neurological examinations have been noted, and no mean changes from baseline in clinical laboratory results have been identified. Overall, there have been only a few clinically significant individual changes from baseline in clinical laboratory measurements in clinical trials of ganaxolone. In the completed placebo-controlled Phase 1, 2 and 3 studies, 0.32% of subjects treated with ganaxolone and 0.31% of subjects treated with placebo exhibited elevated liver function tests during the study (> 3 times the upper limit of normal [ULN] aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]). There have been no cases of Hy's Law in the ganaxolone development program. In controlled clinical trials of ganaxolone, 1.1% of subjects receiving placebo and 2.0% of subjects receiving ganaxolone reported an AE of rash or papular rash. Most rashes improved either while the drug was continued or following discontinuation. Two subjects

participating in the Phase 2 study investigating ganaxolone in treatment of epilepsy developed an SAE of rash. Both events resolved after discontinuation of the study drug.

It is not known if ganaxolone is excreted in breast milk. After cessation of the infusion, plasma ganaxolone levels are expected to drop rapidly, but it is possible that low sub-therapeutic levels persist for several days as ganaxolone is slowly released from tissues. Therefore, a washout period of 45 days is required following cessation of ganaxolone treatment before breast-feeding. Previous toxicology studies in animals focusing on prenatal and neonatal development have not demonstrated toxicities associated with ganaxolone. Ganaxolone has been administered orally to infants with severe forms of epilepsy as early as 4 months of age.

In clinical trials involving administration of oral ganaxolone over several weeks, the study drug has been tapered off over a 1 to 2-week period. There have been no reports of withdrawal symptoms emerging after cessation of ganaxolone.

1.2.2 Ganaxolone: Intravenous Administration

Preclinical studies and a study in 36 healthy volunteers assessing safety, pharmacokinetics (PK), and pharmacodynamics of intravenously (IV) administered ganaxolone have been completed. Preclinical toxicity studies showed IV ganaxolone to be generally safe and AEs consistent with expected dose-related sedation. In rats continuously dosed with IV ganaxolone for 14 days no ganaxolone-related changes were noted in clinical pathology parameters or histopathology examination. There was no evidence of local irritation when ganaxolone was given intra- or perivenously in preclinical studies. Furthermore, IV ganaxolone did not cause hemolysis and was compatible with human plasma.

The safety, PK, and pharmacodynamics of IV ganaxolone were investigated in 36 healthy volunteers in Study 1042-0405, in which ganaxolone was administered as a bolus dose (Stage 1) or as a bolus dose followed by a continuous infusion (Stage 2). Ten of the 36 subjects enrolled were women.

- Stage 1 enrolled and dosed subjects in 4 cohorts (A to D): 6 subjects in Cohort A (10 mg ganaxolone IV bolus in 3 subjects and 30 mg ganaxolone bolus in 3 subjects over 5-minutes), 8 subjects in Cohort B (20 mg ganaxolone bolus over 2-minutes), 8 subjects in Cohort C (30 mg ganaxolone bolus over 1-hour) and 8 subjects in Cohort D (10 mg ganaxolone bolus over 1-hour). Cohorts B, C, and D included 2 placebo subjects in each cohort.
- Stage 2 of the study dosed a total of 6 subjects with a 6 mg bolus followed by a 4-hour infusion at 20 mg/h.

A total of 35 of the 36 subjects enrolled in Stages 1 and 2 completed the study as planned while 1 subject withdrew their consent.

Six subjects reported treatment emergent AEs in Stage 1 and 2. No single AE was seen twice. Only 1 event (headache) was considered by the investigator to be related to ganaxolone. None of the treatment emergent AEs were serious, and all were of mild intensity. No clinically meaningful mean changes in laboratory test results, vital signs, or ECG parameters occurred in any cohort.

Pharmacokinetic data from Study 1042-0405 showed that a bolus infusion of 30 mg ganaxolone over 5-minutes led to peak concentration levels (C_{max}) of > 1,000 ng/ml with no safety concerns. Infusion of 30 mg/h for 1 hour and 20 mg/h for 4 hours led to concentrations of 258 and 215 ng/mL respectively, again without any safety concerns. This is consistent with findings from previous studies with the oral formulation of ganaxolone, in which C_{max} levels of up to 200 to 300 ng/mL were commonly observed and were not associated with major safety findings or toxicity (apart from sedation-related effects).

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Rapidly declining plasma levels of allopregnanolone and other neurosteroids after childbirth are thought to be linked to triggering depression in women who are vulnerable to development of this condition. Ganaxolone, a synthetic analog of allopregnanolone, may provide benefit to these women. This study is intended to explore the safety and efficacy of ganaxolone in women with PPD.

2.2 Study Objectives

2.2.1 Objectives of the Open-label Safety Part

2.2.1.1 Safety Objective

To assess the safety and tolerability of ganaxolone in women with PPD as determined by AEs and changes from baseline in laboratory measures, vital signs, Columbia Suicide Severity Rating Scale (CSSRS), electrocardiogram (ECG), Stanford Sleepiness Scale (SSS), and physical examination.

2.2.1.2 Dosing Objective

To develop an optimal dosing regimen for the double-blind placebo-controlled (DBPC) part of the study. Adverse events and other safety data, including sedation and dosing changes, will be adjudicated by the Data Review Committee (DRC) before proceeding to the DBPC part of the study.

2.2.1.3 Efficacy Objective

To assess the efficacy of ganaxolone using the Hamilton Depression Rating Scale 17-item version (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory 6-item version (STAI6) and Clinical Global Impression-Severity and Improvement (CGI-S and CGI-I) scales.

2.2.1.4 Pharmacokinetic Objective

To collect samples of blood for pharmacokinetic (PK) analysis after administration of oral and IV ganaxolone to use in population-PK analyses, the results of which will be reported separately by the Sponsor.

2.2.2 Objectives of the Double-blind Part

2.2.3 Efficacy Objective

To assess the efficacy of ganaxolone vs placebo using the HAMD17, EPDS, STAI6, CGI-S and CGI-I scales.

The primary efficacy variable in this study is change from baseline in the HAMD17 total score on Day 10 of the DBPC part between ganaxolone and placebo.

2.2.4 Safety Objective

To assess the safety and tolerability of ganaxolone vs placebo in women with PPD as determined by AEs and changes from baseline in laboratory measures, vital signs, CSSRS, ECG, SSS, and physical examination.

2.2.5 Pharmacokinetic Objective

To collect samples of blood for PK analysis after administration of oral doses of ganaxolone. Pharmacokinetics samples will be collected from the subjects participating in the open-label and DBPC parts of the study. These data may be combined with data from other studies for population-PK analyses. If such analyses are conducted, they will be reported separately by the Sponsor.

3 STUDY DESIGN

3.1 Study Design and Study Population

This is a Phase 2, multicenter study in women with PPD consisting of 2 dosing parts: an initial open-label safety part, and a DBPC part.

The investigator has the flexibility to adjust the dose amount and/or timing of dosing if the subject experiences untoward effects during the open-label part, by reducing the dose first to a lower level and possibly increasing it later, if tolerance to the untoward effects develops.

Enrollment and dosing will be completed in the open-label safety part before proceeding to the DBPC part. The goal of the open-label part is to explore the safety of IV and oral ganaxolone in this population, and identify a dosing regimen for the DBPC part.

Open-label Part

For the open-label safety part, approximately 172 women aged 18 to 48 years with PPD will be screened to enroll approximately 88 subjects.

In the first group with approximately 8 subjects, ganaxolone will be titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days. This dosing group is called the open-label 3 times daily (OL TID) group.

The second group with approximately 20 subjects will receive ganaxolone administered at bedtime (QHS). For these subjects, ganaxolone will be titrated to a QHS dose of 675 mg over 4 days, which is then maintained until Day 10, followed by a taper over 4 days. This dosing group is called the OL QHS group.

The third group with approximately 20 subjects will receive ganaxolone administered at a dose of 675 mg QHS for 28 days, followed by a taper over 4 days. This dosing group is called the OL QHS 4-week dosing group.

The fourth group with approximately 20 subjects will receive on the first 2 days, ganaxolone capsules 675 mg at dinner time and 675 mg at bedtime (for a total of 1,350 mg per day on the first 2 days), followed by 26 days of ganaxolone capsules 1,125 mg at dinner time (high fat diet), and a taper over 4 days. This dosing group is called the OL 1,125 mg group.

The fifth group with approximately 20 subjects will receive ganaxolone as IV 12 mg bolus over 2 minutes at approximately 4 pm of the first day, followed by ganaxolone oral suspension 750 mg at dinner time (high fat diet), and 750 mg at bedtime (with a high fat snack) for a total of 1,512 mg on Day 1. On Day 2, subjects will receive ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime, for a total of 1,500 mg, followed by 26 days of ganaxolone oral suspension 1,000 mg at dinner time and a taper over 4 days. This dosing group is called the OL Bolus-oral group.

Double-blind Placebo-controlled Part

For the DBPC part, approximately 100 women with PPD aged 18 to 48 years will be screened to randomize 50 women in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days.

The dosing for the DBPC part of the study will be decided based on the results of the open-label results, and on recommendations from the DRC which is comprised of Marinus' Chief Medical Officer and 2 external physician experts. The total daily dose will not exceed 1600 mg. Randomization will be stratified by the use of concomitant antidepressants so that the number of subjects who are treated with antidepressants and who are not treated with antidepressants will be similar in each treatment group.

3.2 Rationale for Study Design

Rapid changes in allopregnanolone and other neurosteroid levels during and after pregnancy are thought to contribute to the biological underpinnings of PPD. There are also data suggesting that the sensitivity of the GABA system is altered during pregnancy and after childbirth, possibly as a result of changes in the circulating neurosteroid levels, and that there may be a state of neurosteroid withdrawal after pregnancy.[9] Ganaxolone may alleviate PPD by increasing neurosteroid activity.

A previous study with IV allopregnanolone showed that allopregnanolone has the potential to produce a rapid and robust antidepressant activity.[7] We hypothesize that a similar antidepressant activity may be obtained with IV and oral ganaxolone.

Although ganaxolone has been administered to more than 1,500 subjects, there have been no previous studies exploring the safety or efficacy of ganaxolone in PPD or other mood disorders in women.

Various dose amounts, formulations, dosing schemes and treatment durations will be evaluated in the Open-label part to inform the choice of the treatment scheme for the DBPC part.

Approximately 8 or 20 subjects, depending on the group, will receive open-label ganaxolone to evaluate safety, tolerability, kinetics and efficacy of the drug in women diagnosed with PPD. Assessments of AEs, laboratory, ECG, and clinical ratings for safety and efficacy will be gathered to evaluate the possible differential effect of the various dosing schemes.

A double-blind evaluation of safety and efficacy will follow the completion of the open-label part. This study part will utilize a randomized, parallel-group, placebo-controlled design in women diagnosed with PPD. Evaluations of safety and tolerability, as well as efficacy will utilize the same evaluation methods as in the open-label part. The primary efficacy endpoint will be change from baseline in HAMD-17 of active vs placebo treatments. The concomitant use of antidepressants or no use of antidepressants will be stratified 1:1 to enroll similar numbers of subjects in each stratum for both the ganaxolone and placebo treatment groups.

3.3 Dose Selection

Allopregnanolone levels increase gradually throughout pregnancy reaching peak mean concentrations at the end of pregnancy of about 15 to 60 ng/ml. The levels then drop precipitously after delivery.[3, 4, 10] We hypothesize that substitution of the low allopregnanolone levels with ganaxolone would alleviate or reverse the symptoms of PPD. The target trough ganaxolone exposure level of approximately 50 ng/ml was chosen to achieve a level similar to that of allopregnanolone at the end of pregnancy.

Open-label TID dosing group

Ganaxolone doses are titrated for the OL TID dosing group from 225 mg on Day 1 to a daily dose of 900 mg starting on Day 7. Previous studies have shown that the sedating effects of ganaxolone may be minimized via dose titration.

With the proposed dosing regimen for the OL TID dosing group, the ganaxolone mean trough and peak plasma concentrations during the Days 8, 9, and 10 are predicted to fluctuate between 40 ng/ml and 100 ng/ml respectively, based on PK modelling. This dose range is considered to provide adequate ganaxolone plasma exposure from the point of view of testing whether the dose range of 50 to 60 ng/ml is necessary for alleviating the symptoms of PPD. Based on the previous ganaxolone studies, plasma levels below 100 ng/ml have not been sedating in most subjects.

The bedtime doses for the OL TID dosing group are selected to be higher than the daytime doses, and are expected to yield plasma mean peak concentrations up to 180 ng/ml during the night on Days 8, 9 and 10. These levels may be sedating in some subjects. Since disrupted sleep is a hallmark of depression, the potential sleep promoting effect of ganaxolone may in fact be beneficial.

Approximately 8 subjects will be allocated for the OL TID group.

Open-label QHS dosing group

A QHS dosing group is included in the open-label part to explore whether QHS dosing only is well-tolerated and shows comparable therapeutic effect to the TID dosing. In the QHS dosing group, the trough ganaxolone levels are expected to be below 40 ng/ml. However, constant plasma exposures may not be necessary for antidepressant effect but the therapeutic efficacy under this dosing scenario could arise via other mechanisms, such as modulation of sleep architecture.

Approximately 20 subjects will be allocated to the OL QHS group. The enrollment for the OL QHS group will start after all subjects allocated to the OL TID group have started their dosing.

Open-label QHS 4-week dosing group

A QHS 4-week dosing group is included in the open-label part to explore whether administering ganaxolone at 675 mg QHS is well-tolerated and shows sustained therapeutic effect over 4-weeks of dosing, and whether the therapeutic effects are maintained over a 3-month follow-up period.

Approximately 20 subjects will be allocated to the OL QHS 4-week dosing group. The enrollment for the OL QHS 4-week group will start after all subjects allocated to the OL QHS group have started their dosing.

Open-label 1,125 mg dosing group

The OL 1,125 mg dosing group is included in the open-label part to explore whether administering ganaxolone orally at doses up to 1,125 mg per day over 4 weeks (including 1,350 mg in the first 2 days) are safe and well-tolerated and show sustained effects, and whether the therapeutic effects are maintained over a 6-week follow-up period.

The two evening 675 mg oral doses, within 3 hours of each other on Day 1 are expected to provide mean C_{max} plasma concentrations of approximately 250-300 ng/mL, which may be mildly sedating. Twin evening dosing on Day 2 is expected to lead to similar exposure. In previous studies, ganaxolone has been given up to a daily dose of 2000 mg, and at single doses of 1000 mg. Based on previous experience, this dose is expected to be safe.

Approximately 20 subjects will be allocated to the OL 1,125 mg dosing group. The enrollment for the OL 1,125 mg group will start after all subjects allocated to the OL QHS 4-week group have started their dosing.

Open-label IV Bolus-oral dosing group

The OL IV Bolus-oral dosing group is included in the open-label part to explore whether administering IV 12 mg ganaxolone bolus followed by oral suspension dosing of up to 1,000 mg per day (including up to 1,500 mg in the first 2 days) is safe and well-tolerated, and shows sustained therapeutic effect over 4 weeks of dosing, and whether the therapeutic effects are maintained over a 6-week follow-up period.

This initial bolus infusion is targeted to provide a fast onset of antidepressant activity by delivery of rapid plasma exposures to ganaxolone. Together with the two evening 750 mg oral doses within 3 hours of each other, Day 1 dosing is expected to provide mean C_{max} plasma concentrations of approximately 250-300 ng/mL, which may be mildly sedating. Twin evening dosing on Day 2 is expected to lead to similar exposure. In previous studies, ganaxolone has been given up to a daily dose of 2,000 mg, and at single doses of 1,000 mg. Based on previous experience, this dose is expected to be safe.

Approximately 20 subjects will be allocated to the OL Bolus-oral dosing group. The enrollment for the OL Bolus-oral group will start after all subjects allocated to the OL 1,125 mg group have started their dosing.

Dose Justification in the Context of Previous Experience with IV Ganaxolone

In Study 1042-0405, a completed Phase 1 study in healthy volunteers investigating the safety of IV ganaxolone, the highest bolus dose tested was 30 mg, which was infused over 5 minutes (the same rate [6 mg/min] as in the OL Bolus-oral group). This dose led to peak concentration levels (C_{max}) of > 1,000 ng/mL, with no safety concerns (except sedation). This safety profile is consistent with findings from previous studies with the oral formulation of ganaxolone, where

C_{max} levels of up to 200 to 300 ng/mL were commonly observed and were not associated with major safety findings or toxicity (apart from sedation-related effects).

Double-blind Placebo-controlled (DBPC) Part

For the DBPC part of the study, the targeted ganaxolone plasma concentrations and the final dosing formulations will be determined based on the safety and efficacy results of the open-label safety data (Section 3.5). Additional information for the dose-selection for the DBPC part may be obtained from the ongoing phase 2A study in PPD with the ganaxolone IV formulation (conducted under IND No. 106104).

Blinding Scheme

Subjects will be randomized to ganaxolone or placebo in a 1:1 ratio. The randomization scheme will be prepared by an independent third-party vendor. Treatment assignments will be obtained by the investigator (or designee) via an Interactive Voice and/or Web Response System (IxRS). The placebo infusion and placebo capsules are identical to the ganaxolone infusion and capsules, respectively, in their appearance. An unblinded study pharmacist at the investigative site will prepare the ganaxolone and placebo IV solutions and allocate capsule supply for the DBPC part. Members of the DRC will be unblinded. All other study personnel, including persons involved in the evaluation of the study subjects (e.g., investigators, sub-investigators, and physicians/nurses), with the exception of the study pharmacist, will remain blinded at all times, except in case of an emergency. Subjects will be blinded.

3.4 Study Duration

For both the open-label safety OL TID and OL QHS groups, and the DBPC part of the study, the screening period will be up to 2 weeks, followed by a 14-day outpatient treatment period and a 14-day follow-up period. For the OL QHS 4-week dosing group, the screening period will be up to 2 weeks, followed by a 28-day outpatient treatment period, a 4-day taper and a 3-month follow-up period. For the OL 1,125 mg and OL Bolus-Oral dosing groups,the screening period of up to 2 weeks will be followed by a 28-day outpatient treatment period, a 4-day taper, and a 6-week follow-up period (from Day 29).

3.5 Planned Analyses

3.5.1 Analysis After Completion of the Open Label Part

At the completion of the open-label part, adverse events and other safety data, including sedation and dosing changes, will be adjudicated by the DRC before proceeding to the DBPC part of the study. These data will be used to determine the dosing regimen for the DBPC part.

3.5.2 Analyses After Completion of the Double-blind Placebo-controlled Part

After completion of the DBPC part, the data will be evaluated by an independent DRC. Based on the analysis and recommendation by the DRC, the study may be closed at that point, or an additional approximately 50 women with PPD will be treated with ganaxolone or placebo under

a similar study design but using a different dosing regimen. The daily dose may be lowered, increased, or the previous dosing may be repeated.

3.6 Definition of Completion

A dosing group is considered complete when the final subject in the group has completed the final protocol-defined assessment, including follow-up visits for the group.

The Study Completion Date is defined as the date the final subject, across all sites, completes her final protocol-defined assessments for the DBPC part, and includes all follow-up visits.

3.7 Sites and Regions

The study will be conducted in the United States at approximately 30 investigational sites.

4 STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. An understanding of and ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
3. Female aged 18 to 48 years, inclusive, at the Screening Visit
4. Experiencing a major depressive episode, which started between the start of the third trimester and 4 weeks following delivery. The major depressive episode must be diagnosed according to Mini International Neuropsychiatric Interview (MINI) 7.0 interview
5. Given birth in the last 12 months
6. HAMD17 score of ≥ 20 at screening rated by a certified site rater
7. HAMD17 ≥ 18 on Day 1 prior to study drug administration
8. The diagnosis of PPD and severity of depression must be supported by the State versus trait; Assessability; Face validity; Ecological Validity; and Rule of 3 Ps (SAFER) interview
9. Must agree to stop breastfeeding from start of study treatment until 45 days after receiving the last dose of the study drug
10. Must agree to use acceptable contraceptive methods during the study period
11. Must have a reliable family member, significant other or a trusted friend who can take a role as the primary childcare provider and support person at home (including during the night) while the subject is participating in the trial

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Current or past history of any psychotic illness, including major depressive episode with psychotic features
2. Any psychiatric condition that, in the investigator's judgment, is considered clinically significant and could affect subject safety or study outcome including eating disorder, panic disorder, obsessive-compulsive disorder, or post-traumatic stress disorder
3. History of suicide attempt within the past 3 years
4. Active suicidal ideation (e.g., answering "yes" to questions 4 or 5 in the CSSRS suicidal ideation section)

5. History of severe bipolar I disorder (e.g., hospitalization due to the illness, lifetime history of psychosis or suicide attempt)
6. Uncontrolled seizure disorder
7. Current or history within the past 3 years of alcohol or any substance use disorder, with the exception of tobacco or caffeine
8. Positive drug screen for any illicit substances or prescription drugs at screening. If the drug screen is positive for a prescription drug that has the potential to be abused (e.g., amphetamine, benzodiazepine), legitimate use of the drug must be verified by the subject's providing the current pill bottle, prescription for the drug, or a note from the prescribing physician. Cannabis use is prohibited and subjects with positive drug screen for cannabis are excluded. However, occasional users of cannabis may be re-tested after 5 days if the subject is willing to refrain from consuming cannabis-based products during the trial. If the re-test sample is negative at screening the subject can be considered eligible. If the re-test sample is positive for cannabis the investigator may ask for determination of blood levels of Δ9-tetrahydrocannabinol (THC), and its metabolites 11-hydroxy-THC and, 9-carboxy-THC. If THC is not detectable the subject is eligible for the trial.
9. Current or relevant history of any medical disorder that may require treatment or make the subject unlikely to be able to complete the study, or any condition that presents undue risk from the investigational product or procedure point of view
10. Any clinically significant abnormality identified on physical examination, ECG, or laboratory tests, that in the judgment of the investigator would compromise the subject's safety or successful participation in the clinical study
11. Subject has untreated or uncontrolled hypothyroidism
12. Known or suspected intolerance or hypersensitivity to the investigational product(s) or allopregnanolone, or any of the stated ingredients
13. Use of another investigational product within 60 days prior to the first dose of investigational product
14. Has alanine transferase (ALT) or aspartate transferase (AST) greater than 2.5 times upper limit of normal or total bilirubin greater than 1.5 times upper limit of normal (unless elevation is due to Gilbert's syndrome)
15. Screening QT interval Fridericia's correction (QTcF) > 470 msec
16. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or concentrated citrus derived products from diet between screening and last on-treatment visit
17. Receiving concomitant treatment with strong cytochrome P (CYP)3A4 inducers or strong CYP3A4 inhibitors
18. Body mass index (BMI) ≥ 40
19. Subject is pregnant
20. Subject is using prohibited medications as specified in Section 5.3.2

4.3 Reproductive Potential

4.3.1 Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception throughout the study period between screening and last follow-up visit.

Acceptable methods of contraception are:

- Intrauterine device (IUD) plus condoms (If the subject has a hormone-releasing IUD, this must have been in place for a minimum of 30 days)
- Double-barrier methods (e.g., condoms with spermicidal gel, foam or sponge, diaphragm with spermicidal gel, foam or sponge)
- Hysterectomy or tubal ligation at or after delivery

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from the investigational product with the medical monitor when possible. Withdrawn subjects who have not received IP will be replaced.

If the investigational product is discontinued, regardless of the reason, the evaluations listed for Day 10 for OL TID and OL QHS groups or Day 29 for the OL QHS 4-week, OL 1,125 mg, and OL Bolus-oral groups are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-ups. Comments (spontaneous or elicited), complaints, or AEs reported by the subject must be recorded in the source documents. The reason for discontinuation and the date and time of discontinuation of the investigational product must be recorded in the electronic case report form (eCRF) and source documents.

4.4.1 Subject Withdrawal Criteria

All subjects reserve the right to withdraw from the clinical study at any time, as stated in the informed consent form (ICF). The investigator may discontinue subjects from the clinical study for any of the following reasons:

1. Electrocardiogram evidence of QT prolongation (QTcF > 530 msec, or an increase of QTcF > 60 msec above baseline to a value > 480 msec on the 12-lead ECG, confirmed on a repeat 12-lead ECG taken after resting at least 5 minutes in a supine or semi-recumbent position after the original finding of prolonged QTcF).
2. It is the investigator's opinion that it is not in the subject's best interest to continue in the study.
3. Any subject who exhibits any Suicidal Behavior or Suicidal Ideation (e.g., subject answers "yes" to question 4 or 5 in the Suicidal Ideation section of the CSSRS). These subjects should be evaluated by a psychiatrist immediately.

4. Rash that is clinically significant and considered to be related to the study drug (e.g., morbiliform, urticarial, papular).
5. Subject experiences an SAE considered to be related to the study drug

Decisions to discontinue the study will be made at each participating site by the principal investigator. If feasible, the reason for discontinuation should be discussed with the medical monitor.

4.4.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

Reasons for discontinuation include but are not limited to:

- AE
- Protocol deviation
- Withdrawal of consent by subject
- Lost to follow-up
- Lack of efficacy
- Other (If "Other" is selected, the investigator must specify the reason on the eCRF)

4.4.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that she return to the site for final safety evaluations. If contact is made but the subject refuses or is unable to come to the final safety evaluation, it should be documented in the eCRF.

5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatments (including herbal treatments and vitamins) received within 60 days prior to the screening visit (Visit 1) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Pharmacological Treatment

Prior pharmacological treatment includes all treatments (including herbal treatments and vitamins) that the subject received and stopped within 60 days of the date of the screening visit. For example, if the subject had been treated with sertraline during pregnancy but it was discontinued 3 weeks prior to the screening visit, this medication would be recorded on the prior medication eCRF page.

5.2 Concomitant Pharmacological Treatment

Concomitant treatment refers to all treatments (including herbal treatment and vitamins) taken between the screening visit and the end of the follow-up period regardless of the start date of the concomitant medication. For example, if the subject was started on a prenatal vitamin and it was continued through the study period, this treatment would be recorded on the concomitant medication eCRF page.

5.3 Concomitant Psychological Treatment

Concomitant psychological treatment refers to all psychological care the subject received from the time of the screening visit through the end of the follow-up period. Concomitant psychological treatment information must be recorded on the concomitant psychological treatments eCRF page.

5.3.1 Permitted Treatment

5.3.1.1 Permitted Psychological Treatments

The subject may continue their current form of psychological treatment (e.g., cognitive behavioral therapy, psychodynamic psychotherapy, supportive psychotherapy) throughout the treatment period. Initiation of a new therapy (a new treatment modality or switching a therapist) is prohibited during the treatment period. After the treatment period, psychotherapy should be continued using the same modality and at the same frequency as during the treatment period, provided that this is medically justified, in order to be able to determine whether there are sustained effects from the treatment the over the 30-, 42-, or 90-day follow-up periods. Any changes must be recorded on the concomitant psychological treatments eCRF page.

5.3.1.2 Permitted Antidepressant Treatments

The subject may continue their current SSRI, serotonin and norepinephrine reuptake inhibitors, bupropion, other serotonin, or norepinephrine modulating antidepressant (e.g., vortioxetine, mirtazapine) treatment, provided the regimen conforms to the standard of care and the medication was started at least 21 days before the screening visit, and there has not been a dose

change within 7 days of the screening visit. The antidepressant medication must have been approved for treatment of major depressive disorder by the United States (US) Food and Drug Administration (FDA). Monoamine inhibitors are prohibited (including all formulations of selegiline). Tricyclic antidepressant medications will be decided on a case-by-case basis after discussion with the medical monitor.

5.3.1.3 Other Permitted Treatments

The subject may continue her current non-psychiatric medications with the exception of medications that are strong inducers or inhibitors of CYP3A4 (Appendix 1.).

The subject may use diphenhydramine 25 to 50 mg, trazodone 25 to 50 mg, or doxepine 3 to 5 mg for severe insomnia as needed. Only 1 dose of 1 of the medications is allowed per night. Other hypnotics, such as zolpidem or zaleplon, are prohibited.

If the subject is treated with an atypical antipsychotic medication that was started with the purpose of augmenting the therapeutic effect of an antidepressant (i.e., the antipsychotic is not intended for treatment of psychosis or mood stabilization, and it is used in combination with an antidepressant), and the medication has been approved by the US Food and Drug Administration as an add-on therapy for major depression, she may continue this treatment throughout the study period provided that the medication is taken within the approved dose range. Examples of such treatments would be quetiapine 50 mg at bedtime and aripiprazole 10 mg daily. However, the antipsychotic medication must have been started at least 21 days before screening, and there should not have been a dose change within 7 days of screening.

Other medications and medication combinations should be discussed with the medical monitor before enrolling the subject in the study.

After completion of the treatment period, any changes to the antidepressant or antianxiety medication regimen are not prohibited, but investigators are encouraged to maintain such drugs at stable doses if possible. Any changes in the medication regimen must be recorded on the concomitant medication eCRF page.

5.3.2 Prohibited Treatments

The following classes of medications and treatments are prohibited during the study. If the subject has been taking any of these medications before enrollment, there should be a medication-free period of a minimum of 5 days or 5 half-lives of that medication, whichever is longer, before admission to the unit. In general, subjects who require extensive washouts may not be candidates for participation and those cases should be discussed with the medical monitor.

- Benzodiazepines and barbiturates
- Gabapentin and pregabalin
- Anticonvulsants and mood stabilizers
- All hypnotics and sleep aids (with the exception of low-dose diphenhydramine, doxepin, and trazodone as described above)

- Opioids
- Cannabis
- Electroconvulsive Therapy (ECT), rapid transcranial magnetic stimulation (rTMS), vagal nerve stimulation
- Experimental (including hormonal and herbal) treatments of postpartum depression
- Strong inhibitors and inducers of CYP3A4 (Appendix 1.)
- Antipsychotic medications (unless the antipsychotic is used to augment antidepressant medication, is used in combination with an antidepressant, and is approved by the FDA as an add-on therapy for major depression)

6 INVESTIGATIONAL PRODUCTS

6.1 Identity of Investigational Products

6.1.1 Ganaxolone Immediate Release Oral Capsules (0.3 Micron Formulation)

Ganaxolone capsules will be provided in size 00 white/opaque gelatin capsules packaged in high-density polyethylene (HDPE) bottles with a foil induction seal and child resistant closure. Each bottle will contain 28 or 70 capsules. Each capsule contains 225 mg ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one), and hydroxypropyl methylcellulose, sucrose, polyethylene glycol 3350, polyethylene glycol 400, sodium lauryl sulfate, sodium benzoate, citric acid anhydrous, sodium methyl paraben, microcrystalline cellulose, 30% Simethicone Emulsion, gelatin capsules, polysorbate 80, and sodium chloride.

Placebo formulation is comprised of sucrose spheres of comparable size to the ganaxolone spray layered spheres encapsulated in a size 00 white/opaque gelatin capsule. The weights of placebo capsules are matched to ganaxolone capsules. The placebo capsules will be provided to the sites in bottles identical to the active drug.

All study medication will be labeled according to regional regulatory requirements. At a minimum, labels will contain the study number; a blinded bottle number; contents including quantity; dose and form; route of administration; storage conditions; instructions for study drug administration; caution that this compound is an investigative drug intended for clinical trial use only; warning to keep out of reach of children; and the identity of manufacturer and Sponsor. For those regions that require it, a blinded lot number and an expiry date will also be listed.

Ganaxolone and placebo capsules are manufactured by Catalent Inc., Somerset, NJ.

6.1.2 Ganaxolone IV Infusion Solution

Manufacturer: Particle Sciences Inc.

Vehicle: Captisol® containing sterile IV solution

Formulation: IV

Strength: 3 mg/ml solution in a glass vial, which is to be diluted with 0.9% saline for the infusion. For details regarding preparation of the infusion solution, please see pharmacy manual.

Route of administration: IV

6.1.3 Ganaxolone Oral Suspension

Manufacturer: Catalent Pharma Solutions, Somerset, NJ 08873 USA

Vehicle: The oral suspension contains ganaxolone (50 mg/mL), hydroxypropyl methylcellulose, polyvinyl alcohol, sodium lauryl sulfate, simethicone, methylparaben, propylparaben, sodium benzoate, citric acid, and sodium citrate at pH 3.8 to 4.2, and is sweetened with sucralose and flavored with artificial cherry.

Formulation: Oral suspension

Strength: 50 mg/mL oral suspension; 110 mL in 125 mL HDPE bottles

6.2 Administration of Investigational Product(s)

All study medication will be stored at the research pharmacy prior to dispensing, or in a locked cabinet accessible only to members of the investigational research team. Ganaxolone capsules and ganaxolone oral suspension should be stored at room temperature 15°C to 25°C (59°F to 77°F). Ganaxolone stock solution investigational product for IV administration will be stored at refrigerated temperature 2ºC to 8ºC (36ºF to 46ºF). Oral investigational product should be taken within ± 15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado), and with 240 mL (8 oz) of water.

For the IV bolus, ganaxolone 12 mg in 24 mL will be administered over 2 minutes via an indwelling catheter, or a butterfly inserted in a vein on the arm or hand. The investigational product should be given as continuous infusion as instructed. The catheter should be flushed with saline at the end of the bolus infusion. For details, please see pharmacy manual.

6.2.1 Allocation of Subjects to Treatment

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned by the Electronic Data Capture (EDC) system to subjects according to the sequence of presentation for study participation.

In the open-label part, the first approximately 8 subjects will be assigned to OL TID dosing group. After approximately 8 subjects have started dosing in the OL TID group, the dosing for the OL QHS group will commence. Approximately 20 subjects will be dosed for the OL QHS group. After approximately 20 subjects have started dosing in the OL QHS group, the enrollment into the OL QHS 4-week group will commence. After approximately 20 subjects have started dosing in the OL QHS 4-week group, enrollment into the OL 1,125 mg group will commence. Approximately 20 subjects will be dosed for the OL 1,125 mg group. After approximately 20 subjects have started dosing in the OL 1,125 mg group, enrollment into the OL Bolus-oral group will commence. Approximately 20 subjects will be dosed for the OL Bolus-oral group.

In the DBPC part, subjects will be randomized to receive ganaxolone or matching placebo in a 1:1 ratio. Randomization will be stratified by the use of concomitant antidepressants so that the number of subjects who are treated with antidepressants and who are not treated with antidepressants will be similar in each treatment group.

After being enrolled, a subject will be replaced only if she discontinues prior to receiving study treatment.

6.2.2 Dosing for the Open-label Treatment Part – OL TID Group

Subjects start taking the study drug at bedtime (HS) on Day 1 (enrollment). The first dose to be taken will be one 225 mg capsule. The next evening (Day 2), the dose will be increased to 450 mg (2 capsules) to be taken HS. This dose is taken on Day 2 and Day 3.

There will be a study visit on Day 4, which should be scheduled to occur in the morning. On Day 4, the dose is increased to 225 mg QAM (to be started after the study visit) and 450 mg QHS. This dosing (225 mg QAM and 450 mg QHS) is continued on Day 5 and Day 6.

There will be a study visit on Day 7 which should be scheduled to occur in the morning. The morning dose of the study medication on Day 7 should be taken as scheduled before the study visit. The dose will be increased on Day 7 to 225 mg QAM, 225 mg Q2PM and 450 mg QHS. This dose will be continued on Days 8 to 10. The subject should take the new additional afternoon dose that day (Day 7).

There will be a study visit on Day 10, which is the final visit before the taper is started. The visit should occur in the morning of Day 10 before noon. The morning dose of the study drug should be taken as scheduled before the visit.

On Days 11-14, the study drug is tapered off following the schedule in Table 1. The last dose is to be taken on Day 14 QHS.

All doses taken must be recorded in the eCRF.

The study visits are intended to allow evaluation of the subject by the principal investigator and making dose adjustments when necessary. If there have been no adverse events, and the subject has not improved clinically, the investigator should follow the titration schedule and increase the dose.

Table 1. Study Drug Dosing Schedule – Open-Label TID Group

	V2			V3			V4			V5				
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
QAM				225 mg	225 mg	225 mg	225 mg	225 mg	225 mg	225 mg	225 mg	225 mg		
Q2PM							225 mg	225 mg	225 mg	225 mg				
QHS	225 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	450 mg	225 mg
Total	225 mg	450 mg	450 mg	675 mg	675 mg	675 mg	900 mg	900 mg	900 mg	900 mg	675 mg	675 mg	450 mg	225 mg

QAM = approximately 8 am, QHS = approximately 10 pm, or before going to bed for the night

6.2.3 Dosing for the Open-Label Treatment Part – OL QHS Group

Subjects start taking the study drug at bedtime (HS) on Day 1 (enrollment). The first dose to be taken will be one 225 mg capsule. The next evening (Day 2) the dose will be increased to 450 mg (2 capsules) to be taken HS. This dose is taken on Day 2 and Day 3.

There will be a study visit on Day 4, which should be scheduled to occur in the morning. On Day 4, the dose is increased to 675 mg QHS which is continued (through Day 7 visit) until Day 10. There is no planned dose adjustment at Day 7 visit.

There will be a study visit on Day 10, which is the final visit before the taper is started. The visit should occur in the morning of Day 10 before noon.

On Days 11-14 the study drug is tapered off following the schedule in Table 2. The last dose is to be taken on Day 14 QHS.

All doses taken must be recorded in the eCRF.

The study visits are intended to allow evaluation of the subject by the principal investigator and making dose adjustments when necessary. If there have been no adverse events the investigator should follow the dosing schedule.

Table 2. Study Drug Dosing Schedule – Open-Label QHS Group

	V2			V3			V4			V5				
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
QAM														
Q2PM														
QHS	225 mg	450 mg	450 mg	675 mg	675 mg	675mg	675 mg	675 mg	675 mg	675 mg	450 mg	450 mg	225 mg	225 mg
Total	225 mg	450 mg	450 mg	675 mg	675 mg	675 mg	675 mg	675 mg	675 mg	675 mg	450 mg	450 mg	225 mg	225 mg

QAM = approximately 8 am, QHS = approximately 10 pm, or before going to bed for the night

6.2.4 Dosing for the Open-Label Treatment Part – OL QHS Group – 4 Week

Subjects start taking the study drug at bedtime (QHS) on Day 1 (enrollment). The first dose to be taken will be 675 mg (3 capsules), continuing through Day 28 at QHS.

There will be a study visit on Day 2, Day 8, Day 15, and Day 22. There is no planned dose adjustment at any of these visits.

There will be a study visit on Day 29, which is the final visit before the taper is started. The visit should occur in the morning of Day 29 before noon.

On Days 29 to 32 the study drug is tapered off following the schedule in Table 3. The last dose will be taken on Day 32 QHS.

All doses taken must be recorded in the eCRF.

The study visits are intended to allow evaluation of the subject by the principal investigator and making dose adjustments when necessary. If there have been no adverse events the investigator should follow the dosing schedule.

Table 3. Study Drug Dosing Schedule – Open-Label QHS 4 Week Group

	V2	V3	V4	V5	V6	V7			
Day	**1**	**2**	**8**	**15**	**22**	**29**	**30**	**31**	**32**
QHS	675 mg	675 mg	675 mg	675 mg	675 mg	450 mg	450 mg	225 mg	225 mg
Total	675 mg	675 mg	675 mg	675 mg	675 mg	450 mg	450 mg	225 mg	225 mg

There will be total of 11 study visits for the QHS 4-week dosing group: Screening, Day 1, Day 2, Day 8, Day 15, Day 22, Day 29 and 4 safety follow-up visits on Day 36, Day 59, Day 89, and Day 119.

6.2.5 Dosing for the Open-Label Treatment Part – OL 1,125 mg Group

Subjects will start taking ganaxolone capsules, 675 mg (3 capsules) at dinner time (7 pm) followed by 675 mg (3 capsules) at bedtime (HS) on Day 1 and Day 2 followed by 1,125 mg (5 capsules) at dinner time (7 pm) on the next 26 days (Day 3 through Day 28). A 4-day taper will follow: 900 mg (4 capsules) on Day 29, 675 mg (3 capsules) on Day 30, 450 mg (2 capsules) on Day 31, and 225 mg (1 capsule) on Day 32 (Table 4) all at dinner time.

In addition to screening, there will be study visits on days 1, 2, 8, 15, 22, 29, 36, 57, 71.

Day 29 is the final visit before taper is started. The visit should occur in the morning of Day 29 before noon.

All doses taken must be recorded in the eCRF.

The study visits are intended to allow evaluation of the subject by the principal investigator and making dose and/or timing adjustments when necessary (see Section 6.2.7). If there have been no adverse events the investigator should follow the dosing schedule.

Oral ganaxolone should be taken within ± 15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado) and with 240 mL (8 oz) of water.

Table 4. Study Drug Dosing Schedule – Open-label 1,125 mg Group

Visit	**V2**	**V3**		**V4**	**V5**	**V6**	**V7**			
Day	**1**	**2**	**3**	**8**	**15**	**22**	**29**	**30**	**31**	**32**
Q7PM	675 mg	675 mg	1,125 mg	1,125 mg	1,125 mg	1,125 mg	900 mg	675 mg	450 mg	225 mg
QHS	675 mg	675 mg								
Total	1,350 mg	1,350 mg	1,125 mg	1,125 mg	1,125 mg	1,125 mg	900 mg	675 mg	450 mg	225 mg

There will be total of 10 study visits for the OL 1,125 mg dosing group: Screening, Day 1, Day 2, Day 8, Day 15, Day 22, Day 29 and 3 safety follow-up visits on Day 36, Day 57, and Day 71.

6.2.6 Dosing for the Open-Label Treatment Part – OL Bolus-Oral Group

Dosing in the Bolus-Oral group will start with ganaxolone IV bolus 12 mg over 2 minutes at approximately 4 pm on Day 1. Subjects will start taking ganaxolone 750 mg oral suspension (15 mL at 50 mg per mL) at dinner time (7 pm) followed by 750 mg oral suspension at bedtime (HS) on Day 1. On Day 2 subjects will again take 750 mg oral suspension at dinner time (7 pm) followed by 750 mg at bedtime (HS). For the following 26 days (Day 3 through Day 28) subjects will take ganaxolone 1,000 mg oral suspension (20 mL at 50 mg per mL) at dinner time (7 pm). A 4-day taper will follow: 750 mg (15 mL) on Day 29, 500 mg (10 mL) on Day 30, 500 mg (10 mL) on Day 31, and 250 mg (5 mL) on Day 32 (Table 5) all at dinner time.

In addition to screening, there will be study visits on days 1, 2, 8, 15, 22, 29, 36, 57, 71.

Day 29 is the final visit before taper is started. The visit should occur in the morning of Day 29 before noon.

All doses taken must be recorded in the eCRF.

The study visits are intended to allow evaluation of the subject by the principal investigator and making dose and/or timing adjustments when necessary (see Section 6.2.7). If there have been no AEs, the investigator should follow the dosing schedule.

Oral ganaxolone should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado) and with 240 mL (8 oz) of water.

Table 5. Study Drug Dosing Schedule – Open-label Bolus-oral Group

Visit	**V2**	**V3**		**V4**	**V5**	**V6**	**V7**			
Day	**1**	**2**	**3**	**8**	**15**	**22**	**29**	**30**	**31**	**32**
4PM	12 mg IV Bolus									
Q7PM	750 mg	750 mg	1,000 mg	1,000 mg	1,000 mg	1,000 mg	750 mg	500 mg	500 mg	250 mg
QHS	750 mg	750 mg								
Total	1,512 mg	1,500 mg	1,000 mg	1,000 mg	1,000 mg	1,000 mg	750 mg	500 mg	500 mg	250 mg

There will be total of 10 study visits for the OL Bolus-Oral dosing group: Screening, Day 1, Day 2, Day 8, Day 15, Day 22, Day 29 and 3 safety follow-up visits on Day 36, Day 57, and Day 71.

6.2.7 Dose Adjustments During Open-label

Adjusting doses for the OL TID dosing group

During the study the investigator has the opportunity to de-escalate, skip dose escalation and re-escalate during the titration on Days 1 to 10 at the scheduled study visits if the subject is experiencing adverse events. The dose adjustments done at the study visits should follow the schedule outlined in Table 1. The investigator should de-escalate to a previous dosing schedule, repeat the current dosing schedule or re-escalate to dosing scheme outline in the table. Other flexible adjustments are not allowed.

Example 1:

If the subject at Day 4 visit reports adverse effects (e.g., sedation) with the 450 mg QHS dose, the investigator may decrease the dose to 225 mg QHS (de-escalation) or continue the 450 mg QHS dose (skip dose escalation). The investigator may then attempt to re-escalate the dose to the next dose level at the next visit (Day 7). If the investigator opted to maintain the 450 mg QHS dose at the Day 4 visit, the investigator may then increase the dose to the next scheduled dose level (225 mg QAM and 450 mg QHS) at Day 7 visit provided that the subject has developed a tolerance to the sedative effects.

Example 2:

If the subject at study visit on Day 7 reports intolerable sedation after the morning dose, the investigator may choose to drop the dosing to 450 mg QHS or skip the escalation and maintain the current dosing (225 mg QAM and 450 mg QHS).

Subjects who do not reach the 900 mg daily dose (225 mg QAM, 225 mg Q2PM and 450 mg QHS) will be tapered off the study medication by reducing the dose by about 225 mg per day or every other day over the Days 11 to 14. The QHS dose should be the last dose before the drug is discontinued completely.

The subjects who do not tolerate the first dose of 225 mg QHS should be considered for discontinuation.

All doses taken must be recorded in the eCRF.

If the study visit falls on the weekend, or if the subject is not able to come to the study scheduled study visit, each visit has a window + 3 days. Under this scenario, the subject would continue at the prescribed dose level until the study visit.

Adjusting doses for the OL QHS dosing group

During the study the investigator has the opportunity to defer a dose escalation to 675 mg at Day 4 Visit if the subject reports adverse events (e.g., sedation in the morning) and attempt escalation at Day 7 Visit or continue the dosing at 450 mg QHS until Day 10 Visit.

Adjusting doses for the OL QHS 4 week dosing group

The investigator has the flexibility to adjust treatment reducing the dose to one or two capsules, if the subject experiences sedation, dizziness or other untoward effects during the OL part.

Adjusting dose and/or timings for the OL 1,125 mg dosing group

The investigator has the flexibility to adjust dose by reducing the dose to 450 mg (2 capsules) at the second of Day 1 doses (at HS) and/or at either of Day 2 doses, and/or reduce to 900 mg, 675 mg, or 450 mg on Day 3 through Day 28 (at dinner time) if subject experiences sedation, dizziness or other untoward effects during the OL part. The investigator can also change the timing of the evening dose bringing it closer to bedtime and taking it with a fatty snack instead of dinner. Any further adjustments as well as adjusted taper period doses should be discussed with the medical monitor. The investigator may increase the dose back to default levels if tolerance develops to the untoward effects.

Adjusting dose and/or timings for the OL Bolus-oral dosing group

The investigator has the flexibility to adjust dose by reducing the dose to 500 mg (10 mL) for the second of Day 1 doses (at HS) and/or either of Day 2 doses, and/or reduce to 750 mg (15 mL), or 500 mg (10 mL) at dinner time on Day 3 through Day 28 if subject experiences sedation, dizziness or other untoward effects during the OL part. The investigator can also change the timing of the evening dose bringing it closer to bedtime and taking it with a fatty snack instead of dinner. Any further adjustments as well as adjusted taper period doses should be discussed with the medical monitor. The investigator may increase the dose back to default levels if tolerance develops to the untoward effects.

6.2.8 Blinding

During the DBPC part, subjects randomized to placebo will receive placebo capsules which are identical to the active ganaxolone capsules.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

Bottles will be labeled before shipping to the sites. In the DBPC part, the contents of each bottle will be blinded using labels. The randomization schedule will match a subject number to a bottle number.

6.3.2 Packaging and Dispensing the Study Drug

Ganaxolone capsules and matching placebos will be provided in HDPE bottles.

All packaging and labeling operations will be performed according to good manufacturing practice (GMP) and good clinical practice (GCP) guidelines. Investigational products are prepared and distributed by the site pharmacist.

The site pharmacy or delegated site staff will be responsible for dispensing the study treatment to the subject. Sufficient amount of supplies will be provided to the subject until the next study visit and a minimum of 3 days' overage to cover for weekends, study site closures and unexpected need for rescheduling the study visit.

Detailed instructions on when to take the medication and a reminder to take oral study medication within ± 15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado) and with 240 mL (8 oz) of water will be provided to the subject.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational products are stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacist, but this delegation must be documented.

The ganaxolone stock solution investigational product for the IV administration will be stored at refrigerated temperature 2ºC to 8ºC (36ºF to 46ºF).

The 0.3-micron ganaxolone capsules (225 mg), oral suspension, and matching placebos are stored in HDPE bottles with a foil induction seal and child resistant closure at room temperature (15ºC to 25ºC; 60ºF to 75ºF).

Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained. The temperature should be monitored continuously through use of either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. The sponsor or sponsor's delegate must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor or sponsor's delegate should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

6.4 Drug Accountability

Drug kits containing the study drug and supplies needed for each subject for the entire study will be supplied to the investigational site by the sponsor or a distributor on behalf of the sponsor. The pharmacist or delegated site staff will inventory and acknowledge receipt of all shipments of the kits. The study drugs must be kept in a locked area with restricted access and stored and handled in accordance with the manufacturers' instructions. The pharmacist will also keep

accurate records of the quantities of study drug dispensed and used. The pharmacist is responsible for all drug supplies; written documentation is mandatory. The study monitor will periodically check the supplies of the study drug held by the pharmacist to verify accountability of all kits used. The pharmacist will dispense the study drug according to the dosing plan. Upon receiving study drugs, the principal investigator and the team members will administer them only to the identified subjects in this study, following the procedures described in this study protocol and documented in the appropriate eCRF. At the conclusion of the study, all unused study drug will be returned or destroyed per the site's Standard Operating Procedures (SOP) or instructions from the sponsor. The sponsor will verify that a final report of drug accountability to the unit-dose level is prepared and maintained in the principal investigator's study file.

6.5 Drug Administration

Oral doses of the investigational product should be taken within ±15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado), and with 240 mL (8 oz) of water.

For the IV bolus ganaxolone 12 mg in 24 mL will be administered over 2 minutes via an indwelling catheter or a butterfly, inserted in a vein on the arm or hand. The investigational product should be given as continuous infusion as instructed. The catheter should be flushed with saline at the end of the bolus infusion. For details please see pharmacy manual. Subjects will be informed about possible side effects from the study medication and cautioned to avoid quick postural changes. They should not carry the baby or sleep with the baby in the same bed due to the possible side-effect of dizziness and sedation. Subjects will be advised not to drive, operate heavy machinery, or participate in any potentially hazardous activity during the study that requires full mental alertness until they are sure the medication is not affecting alertness. They will also be cautioned that non-adherence to the dosing instructions (e.g., increasing the dose, taking the study medication doses too close together) could produce side effects.

The interaction between alcohol and ganaxolone is not known. Alcohol use is prohibited during the treatment period.

The subject must have a reliable family member, significant other or a trusted friend who can take the role for being the primary childcare provider and a support person at home (including at nighttime) while the subject is participating in the trial, including for subjects who may stay overnight on the unit as part of the screening process and/or the PK subgroup.

7 STUDY PROCEDURES

This is a Phase 2, multicenter study in women with postpartum depression (PPD) consisting of 2 dosing parts: an initial open-label safety part and a DBPC part.

For the open-label safety part, approximately 172 women 18 to 48 years of age with PPD will be screened to enroll approximately 88 subjects. During this open-label safety part, for the first approximately 8 subjects, ganaxolone will be titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days. This dosing group is called OL TID group.

For the next approximately 20 subjects, ganaxolone will be administered at QHS. For these subjects, ganaxolone will be titrated to a QHS dose of 675 mg over 4 days which is then maintained until day 10, followed by a taper over 4 days. This dosing group is called OL QHS group.

For the next approximately 20 subjects, ganaxolone will be administered at bedtime (QHS). For these subjects ganaxolone treatment will be a QHS dose of 675 mg over 28 days, followed by a taper over 4 days. This dosing group is called OL QHS 4-week group.

The next approximately 20 subjects of the open-label safety part will receive on the first 2 days ganaxolone capsules 675 mg at dinner time and 675 mg at bedtime (for a total of 1,350 mg per day on the first 2 days) followed by 26 days of ganaxolone capsules 1,125 mg at dinner time, followed by a taper over 4 days. This dosing group is called OL 1,125 mg group.

For the next approximately 20 subjects of the open-label safety part, ganaxolone will be administered as IV bolus 12 mg over 2 minutes at approximately 4 pm on Day 1 followed by ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime, for a total of 1,512 mg on the first day. On Day 2 subjects will receive ganaxolone oral suspension 750 mg at dinner time and at 750 mg at bedtime, for a total of 1,500 mg, followed by 26 days of ganaxolone oral suspension 1000 mg at dinner time, followed by a taper over 4 days. This dosing group is called OL Bolus-Oral group. The investigator has the flexibility to adjust the dose and/or timing of the dose if the subject experiences sedation, dizziness or other untoward effects during the OL part (see Section 6.2.7).

The open-label safety part will be enrolled, and dosing completed before proceeding to the DBPC part. The goal of the open-label part is to explore safety of IV and oral ganaxolone in this population and identify a dosing regimen for the DBPC part.

For the DBPC part, approximately 100 women with PPD 18 to 48 years of age will be screened to randomize 50 women in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days. The dosing for the DBPC portion of the study will be decided based on the results of the open-label portion and recommendations of the DRC. The DRC is comprised of Marinus' Chief Medical Officer and 2 external physician experts. The daily dose will not exceed 1,600 mg. Randomization will be stratified by the use of concomitant antidepressants so that the number of subjects who are treated with antidepressants and who are not treated with antidepressants will be similar in each treatment group.

7.1 Screening Period (Day -14 to -1) for OL TID and OL QHS

7.1.1 Screening Visit (Visit 1)

- Obtain written informed consent
- Collect demographics, medical history, review prior medications, review of concomitant medications and therapies,
- Assess CGI-S
- Conduct Mini International Neuropsychiatric Interview 7.0 (MINI 7.0)
- Conduct HAMD17 interview (if a HAMD17 interview was conducted for Marinus PPD study 1042-PPD-2002 at the same investigative site within 2 weeks of the screening visit the screening HAMD17 interview does not have to be repeated).
- Perform EPDS
- Perform STAI6
- Perform a physical examination
- Collect vital signs (blood pressure [BP], pulse, temperature, respiratory rate [RR])
- Collect ECG
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Collect safety laboratory tests
- Measure height and weight
- Conduct CSSRS interview
- Review inclusion and exclusion criteria. Screen failure is defined as a subject who has given informed consent, and failed to meet the inclusion criteria and/or met the exclusion criteria
- Schedule a SAFER interview if the subject meets the eligibility criteria. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study (if a SAFER interview was conducted within 2 weeks for Marinus PPD study 1042-PPD-2002 at the same investigative site the SAFER interview does not have to be repeated. In this instance the HAMD17 score from the SAFER interview can be used to qualify the subject for the study).
- Screening period may be extended to 21 days with approval from the medical monitor (e.g., a laboratory sample was hemolyzed and had to be repeated causing a delay).

7.2 Treatment Period (Day 1 to Day 14; Visits 2 to 5) for OL TID and OL QHS

7.2.1 Start of the Open-label Safety Period (Day 1; Visit 2)

- The subject arrives in the clinic to complete baseline assessments on Day 1.
- Conduct HAMD17 interview
- Perform EPDS
- Perform STAI6

- Assess CGI-S
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- Measure weight
- Collect ECG
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Collect safety laboratory tests
- Collect neurosteroid level
- Collect SSS
- Collect AEs
- Conduct CSSRS interview
- Review inclusion and exclusion criteria (including hematology, chemistry, urinalysis, urine drug screen and pregnancy tests from the screening visit); HAMD17 must be ≥ 18 for enrollment.
- If the subject continues to meet the inclusion criteria and has not developed any exclusion criteria the subject will be enrolled in the study.
- Dispense medication after enrollment to the open-label. Provide the subject with dosing instructions.
- The subject will be instructed to take the first dose of the study medication that night (225 mg)
- If the subject is breastfeeding, she is encouraged to "pump and dump" during the study period and for 45 days after the last dose. She should be provided with a breast pump if she does not have one. Breast feeding is prohibited during the treatment phase and until 45 days following the last dose of the study drug.

7.2.2 Treatment Visits (Days 4, 7, 10) (+ 3 days) for OL TID and OL QHS

- Conduct interviews for HAMD17
- Conduct interviews for CGI-I
- EPDS
- STAI6
- Collect AEs
- Collect ECG (Day 7, Day 10)
- Collect vital signs (BP, pulse, RR, temperature)
- Collect SSS
- Collect a PK sample
- Record concomitant medications
- Collect safety laboratory tests (Day 10 only)
- Collect neurosteroid level (Day 10 only)

- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Conduct CSSRS interview
- Perform a physical examination and collect weight (Day 10 only)
- Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions.
- Start study drug taper on Day 11

7.3 Follow-up Visit 1 (Day 17 ± 2) and Follow-up Visit 2 (Day 38 ± 4) for OL TID and OL QHS

- The Follow-up Visit 1 should occur about 1 week after D10 visit, and about 3 days after the subject has taken her last dose of the study medication. The Follow-up Visit 2 should occur approximately 3 weeks after Follow-up Visit 1 (unless there is a medical need to see the subject sooner; an additional safety visit can be scheduled as per the investigator's discretion).
- Conduct interviews for HAMD17 and CGI-I
- Perform EPDS
- Perform STAI6
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- Collect safety laboratory tests (Follow-up Visit 1 only)
- Collect neurosteroid level (Follow-up Visit 1 only)
- Collect PK sample
- Collect urine for urinalysis, urine drug screen, and urine pregnancy test
- Measure weight
- Conduct CSSRS interview
- Collect SSS
- Collect AEs

Table 6. Schedule of Assessments for the Open-label OL TID and OL QHS and Double-blind Groups

VISIT	Screening (V1)	Day1 (V2)	Day4 (V3)	Day7 (V4)	D10 (V5)	Day17 (V6, 1st FU)	Day38 (V7, 2nd FU)
Informed consent	X						
Demographics, medical history	X						
MINI neuropsychiatric interview	X						
Inclusion/Exclusion criteria	X	X					
Randomize patient (DB only)		X					
Dispense medication		X	X	X	X		
Concomitant Medications and Prior Therapy Review	X	X	X	X	X	X	X
Physical examination	X				X		
SAFER Interview (during screening)	X						
Vital signs (BP, Pulse, RR, temperature)	X	X	X	X	X	X	X
Height (screening only) and weight	X	X			X	X	X
ECGs	X	X		X	X		
Safety Laboratory Tests	X	X			X	X	
Neurosteroid sample collection		X			X	X	
Urinalysis Drug Screen and Pregnancy Tests	X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X
PK sample collection			X	X	X	X	X
HAMD17	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X
CGI-S	X	X					
EPDS	X	X	X	X	X	X	X
STAI6	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X
SSS		X	X	X	X	X	X
Start Taper					X		

The following priority order will be in effect when more than 1 assessment is required at a particular time point: 1) HAMD17 2) CGI-I/CGI-S 3) EPDS 4) STAI6 5) SSS 6) CSSRS 7) vital signs 8) ECG 9) safety labs 10) neurosteroid sample 11) PK sample 12) urinalysis, urine drug screen and pregnancy test 13) physical examination. SAFER interview is scheduled if subject meets the eligibility criteria at the Screening visit. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study. Screening period may be extended to 21 days with approval from the medical monitor.

7.4 Screening Period (Day -14 to -1) for OL QHS 4 week

7.4.1 Screening Visit (Visit 1)

- Obtain written informed consent
- Collect demographics, medical history, review prior medications, review of concomitant medications and therapies,
- Assess CGI-S
- Conduct Mini International Neuropsychiatric Interview 7.0 (MINI 7.0)
- Conduct HAMD17 interview (if a HAMD17 interview was conducted for Marinus PPD study 1042-PPD-2002 at the same investigative site within 2 weeks of the screening visit the screening HAMD17 interview does not have to be repeated).
- Perform EPDS
- Perform STAI6
- Perform a physical examination
- Collect vital signs (blood pressure [BP], pulse, temperature, respiratory rate [RR])
- Collect ECG
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Collect safety laboratory tests
- Measure height and weight
- Conduct CSSRS interview
- Review inclusion and exclusion criteria. Screen failure is defined as a subject who has given informed consent, and failed to meet the inclusion criteria and/or met the exclusion criteria
- Schedule a SAFER interview if the subject meets the eligibility criteria. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study (if a SAFER interview was conducted within 2 weeks for Marinus PPD study 1042-PPD-2002 at the same investigative site the SAFER interview does not have to be repeated. In this instance the HAMD17 score from the SAFER interview can be used to qualify the subject for the study).
- Screening period may be extended to 21 days with approval from the medical monitor (e.g., a laboratory sample was hemolyzed and had to be repeated causing a delay).

7.5 Treatment Period (Day 1 to Day 28; Visits 2 to 7) for OL QHS 4 week

7.5.1 Start of the Open-label Safety Period (Enrollment Visit for the OL QHS 4 week) (Day 1)

- The subject arrives in the clinic to complete baseline assessments on Day 1.
- Conduct HAMD17 interview
- Perform EPDS
- Perform STAI6

- Assess CGI-S
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- Measure weight
- Collect ECG
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Collect safety laboratory tests
- Collect neurosteroid level
- Collect SSS
- Collect AEs
- Conduct CSSRS interview
- Review inclusion and exclusion criteria (including hematology, chemistry, urinalysis, urine drug screen and pregnancy tests from the screening visit); HAMD17 must be ≥ 18 for enrollment.
- If the subject continues to meet the inclusion criteria and has not developed any exclusion criteria the subject will be enrolled in the study
- Dispense medication bottle after enrollment to the open-label Provide the subject with dosing instructions and subject diary completion.
- The subject will be instructed to take the first dose of the study medication that night (675 mg for the OL QHS 4 week group)
- If the subject is breastfeeding, she is encouraged to "pump and dump" during the study period and for 45 days after the last dose. She should be provided with a breast pump if she does not have one. Breast feeding is prohibited during the treatment phase and until 45 days following the last dose of the study drug.

7.5.2 Treatment Visits (Days 2, 8, 15, 22, 29) for OL QHS 4 week

- Conduct interviews for HAMD17
- Conduct interviews for CGI-I
- EPDS
- STAI6
- Collect AEs
- Collect ECG (Day 7, Day 14)
- Collect vital signs (BP, pulse, RR, temperature)
- Collect SSS
- Collect a PK sample
- Record concomitant medications
- Collect safety laboratory tests (Day 14 only)
- Collect neurosteroid level (Day 14 only)

- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Conduct CSSRS interview
- Perform a physical examination and collect weight (Day 14 only)
- Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions.
- Start study drug taper Day 29-32

7.6 Follow-up Visit 1 (Day 36 ± 2), Follow-up Visit 2 (Day 59 ± 2), Follow-up Visit 3 (Day 89 ± 4), and Follow-up Visit 4 (Day 119 ± 4) for the OL QHS 4 week group

- The Follow-up Visit 1 should occur about 1 week after D29 visit, and about 4 days after the subject has taken her last dose of the study medication. The Follow-up Visit 2 should occur approximately 30 days after Follow-up Visit 1. The Follow-up Visit 3 should occur approximately 30 days after Follow-up Visit 2. The Follow-up Visit 4 should occur approximately 30 days after Follow-up Visit 3. (All Follow-up visits should be scheduled within visit window unless there is a medical need to see the subject sooner; an additional safety visit can be scheduled as per the investigator's discretion)
- Conduct interviews for HAMD17 and CGI-I
- Perform EPDS
- Perform STAI6
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- ECG (Follow-up Visit 1 only)
- Collect safety laboratory tests (Follow-up Visit 1 and 2 only)
- Collect neurosteroid level (Follow-up Visit 1 and 2 only)
- Collect PK sample (Follow-up Visit 1 and 2 only)
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Measure weight (Follow-up Visit 4 only)
- Conduct CSSRS interview
- Collect SSS
- Collect AEs
- Collect study medication bottle dispensed at Day 29 (Follow-up Visit 1 only). Review subject dosing diary and complete drug accountability while subject is present.

Table 7. Schedule of Assessments for the Open-label OL QHS 4 Week Group

VISIT	Screening (V1)	Day1 (V2)	Day2 (V3)	Day8 (V4)	D15 (V5)	Day22 (V6)	Day29 (V7)	Day36 (V8; 1st FU)	Day59 (V9; 2nd FU)	Day89 (V10; 3rd FU)	Day 119 (V11; 4th FU)
Informed consent	X										
Demographics, medical history	X										
MINI neuropsychiatric interview	X										
Inclusion/Exclusion criteria	X	X									
Dispense medication / Return Accountability		X	X	X	X	X	X	X			
Concomitant Medications and Prior Therapy Review	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X						X				
SAFER Interview (during screening)	X										
Vital signs (BP, Pulse, RR,	X	X	X	X	X	X	X	X	X	X	X
Height (screening only) and weight	X	X					X				X
ECGs	X				X		X	X			
Safety Laboratory Tests	X	X			X		X	X	X		
PK sample collection			X	X	X		X	X	X		
Neurosteroid sample collection		X	X	X	X		X	X	X		
Urinalysise Drug Screen and Pregnancy	X	X		X	X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X	X	X	X
HAMD17	X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X
CGI-S	X	X									
EPDS	X	X	X	X	X	X	X	X	X	X	X
STAI6	X	X	X	X	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X	X	X	X	X
SSS		X	X	X	X	X	X	X	X	X	X
Start Taper							X				

The following priority order will be in effect when more than 1 assessment is required at a particular time point: 1) HAMD17 2) CGI-I/CGI-S 3) EPDS 4) STAI6 5) SSS 6) CSSRS 7) vital signs 8) ECG 9) safety labs 10) neurosteroid sample 11) PK sample 12) urinalysis, urine drug screen and pregnancy test 13) physical examination. SAFER interview is scheduled if subject meets the eligibility criteria at the Screening visit. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study. Screening period may be extended to 21 days with approval from the medical monitor.

7.7 Screening Period (Day -14 to -1) for OL 1,125 mg and OL Bolus-Oral groups

7.7.1 Screening Visit (Visit 1)

- Obtain written informed consent
- Collect demographics, medical history, review prior medications, review of concomitant medications and therapies,
- Assess CGI-S
- Conduct Mini International Neuropsychiatric Interview 7.0 (MINI 7.0)
- Conduct HAMD17 interview (if a HAMD17 interview was conducted for Marinus PPD study 1042-PPD-2002 at the same investigative site within 2 weeks of the screening visit the screening HAMD17 interview does not have to be repeated).
- Perform EPDS
- Perform STAI6
- Perform a physical examination
- Collect vital signs (blood pressure [BP], pulse, temperature, respiratory rate [RR])
- Collect ECG
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Collect safety laboratory tests
- Measure height and weight
- Conduct CSSRS interview
- Review inclusion and exclusion criteria. Screen failure is defined as a subject who has given informed consent, and failed to meet the inclusion criteria and/or met the exclusion criteria
- Schedule a SAFER interview if the subject meets the eligibility criteria. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study (if a SAFER interview was conducted within 2 weeks for Marinus PPD study 1042-PPD-2002 at the same investigative site the SAFER interview does not have to be repeated. In this instance the HAMD17 score from the SAFER interview can be used to qualify the subject for the study).
- Screening period may be extended to 21 days with approval from the medical monitor (e.g., a laboratory sample was hemolyzed and had to be repeated causing a delay).

7.8 Treatment Period (Day 1 to Day 29; Visits 2 to 7) for OL 1,125 mg and OL Bolus-Oral groups

7.8.1 Start of the Open-label Safety Period (Enrollment Visit for the OL 1,125 mg and OL Bolus-Oral groups) (Day 1)

- The subject arrives in the clinic to complete baseline assessments on Day 1.
- CTNI to conduct HAMD17 interview
- Perform EPDS

- Perform STAI6
- Assess CGI-S
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- Measure weight
- Collect ECG
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Collect safety laboratory tests
- Collect neurosteroid level
- Collect SSS
- Collect AEs
- Conduct CSSRS interview
- Review inclusion and exclusion criteria (including hematology, chemistry, urinalysis, urine drug screen and pregnancy tests from the screening visit); HAMD17 (as determined by CTNI) must be ≥ 18 for enrollment.
- If the subject continues to meet the inclusion criteria and has not developed any exclusion criteria the subject will be enrolled in the study
- Dispense medication bottle after enrollment. Provide the subject with dosing instructions and subject diary completion.
- For the OL 1,125 mg group: the subject will be instructed to take the first oral doses of the study medication that evening (675 mg [3 capsules] at dinner time [at 7 pm] and at bedtime [at 10 pm])
- For the OL Bolus-Oral group: the subject will receive IV bolus 12 mg over 2 minutes at approximately 4 pm (preferably ±1 hour) while on the unit, be observed for development of sedation and/or other untoward effects for at least 1 hour post-bolus and then be discharged and instructed to take the first oral doses of the study medication that evening (750 mg [15 mL oral suspension at 50 mg per mL] at dinner time [at 7 pm] and at bedtime [at 10 pm])
- Oral IP should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado), and with 240 mL (8 oz) of water.
- A sub-group of 6 subjects (to be called 'PK sub-group', Section 7.10.7) in each of the OL 1,125 mg and OL Bolus-Oral groups will stay overnight on the unit between Day 1 and Day 2 to undergo comprehensive PK assessment as follows: for the OL 1,125 mg group plasma samples for PK analysis will be drawn at the following times after the first oral dose on Day 1 (i.e., the 675 mg oral capsules dose at 7 pm at dinner time; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the 10 pm 675 mg dose), at +4hr, +5hr, +6hr, and at 8 am on Day 2. For the OL Bolus-Oral group plasma samples for PK analyses will be drawn at the following times after the IV bolus on Day 1 (e.g., the 12 mg IV bolus at 4 pm; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the first oral dose of 750 mg oral suspension at dinner time), at +4hr, +5hr, +6hr (i.e., just prior to the second 750 mg oral suspension evening dose), at + 7hr, +8hr, and at 8 am on Day 2.

- If the subject is breastfeeding, she is encouraged to "pump and dump" during the study period and for 45 days after the last dose. She should be provided with a breast pump if she does not have one. Breast feeding is prohibited during the treatment phase and until 45 days following the last dose of the study drug.

7.8.2 Treatment Visits (Days 2, 8, 15, 22, 29 ± 3 days [except Day 2]) for OL 1,125 mg and OL Bolus-Oral groups

- CTNI to conduct interview for HAMD17
- Conduct interview for CGI-I
- EPDS
- STAI6
- Collect AEs
- Collect ECG (Day 2, Day 8, Day 15, Day 29)
- Collect vital signs (BP, pulse, RR, temperature)
- Measure weight (Day 15, Day 29)
- Collect SSS
- Collect a PK sample
- Record concomitant medications
- Collect safety laboratory tests (Day 15, Day 29)
- Collect neurosteroid level (Day 2, Day 8, Day 15, Day 29)
- Collect urine for urinalysis, urine drug screen and urine pregnancy test (Day 8, Day 15, Day 22, Day 29)
- Conduct CSSRS interview
- Perform a physical examination (Day 29)
- Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions.
- For the OL 1,125 mg group: the subject will be instructed to take Day 2 oral doses of the study medication that evening (675 mg [3 capsules] at dinner time [at 7 pm] and 675 mg [3 capsules] at bedtime [at 10 pm]) followed by 26 days of 1,125 mg (5 capsules) at dinner time
- For the OL Bolus-Oral group: the subject will be instructed to take Day 2 oral doses of the study medication that evening (750 mg [15 mL oral suspension at 50 mg per mL] at dinner time [at 7 pm] and 750 mg [15 mL oral suspension at 50 mg per mL] at bedtime [at 10 pm]) followed by 26 days of 1,000 mg (20 mL oral suspension at 50 mg per mL) at dinner time
- Oral IP should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado), and with 240 mL (8 oz) of water.
- During Visit 7 (Day 29) start study drug taper (Day 29-32) (See Sections 6.2.5 and 6.2.6)

7.9 Follow-up Visit 1 (Day 36 ± 3), Follow-up Visit 2 (Day 57 ± 3), and Follow-up Visit 3 (Day 71 ± 3) for the OL 1,125 mg and OL Bolus-Oral groups

- The Follow-up Visit 1 should occur about 1 week after D29 visit, and about 4 days after the subject has taken her last dose of the study medication. The Follow-up Visit 2 should occur approximately 21 days after Follow-up Visit 1. The Follow-up Visit 3 should occur approximately 14 days after Follow-up Visit 2 (All Follow-up visits should be scheduled within visit window unless there is a medical need to see the subject sooner; an additional safety visit can be scheduled as per the investigator's discretion).
- CTNI to conduct interview for HAMD17
- Conduct interview for CGI-I
- Perform EPDS
- Perform STAI6
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- ECG (Follow-up Visit 1 only)
- Collect safety laboratory tests (Follow-up Visit 1 and 3 only)
- Collect neurosteroid level (Follow-up Visit 1 and 3 only)
- Collect PK sample (Follow-up Visit 1 only)
- Collect urine for urinalysis, urine drug screen and urine pregnancy test
- Measure weight (Follow-up Visit 3 only)
- Conduct CSSRS interview
- Collect SSS
- Collect AEs
- Collect study medication bottle dispensed at Day 29 (Follow-up Visit 1 only). Review subject dosing diary and complete drug accountability while subject is present.

Table 8. Schedule of Assessments for the Open-label OL 1,125 mg and OL Bolus-oral Groups

VISIT	Screening (V1)	Day1 (V2)	Day2 (V3)	Day8 ±3d (V4)	D15 ±3d (V5)	Day22 ±3d (V6)	Day29 ±3d (V7)	Day36 ±3d (V8; 1st FU)	Day57 ±3d (V9; 2nd FU)	Day71 ±3d (V10; 3rd FU)
Informed consent	X									
Demographics, medical history	X									
MINI neuropsychiatric interview	X									
Inclusion/Exclusion criteria	X	X								
Dispense medication / Return Accountability		X	X	X	X	X	X	X		
Concomitant Medications and Prior Therapy Review	X	X	X	X	X	X	X	X	X	X
Physical examination	X						X			
SAFER Interview (during screening)	X									
Vital signs (BP, Pulse, RR,	X	X	X	X	X	X	X	X	X	X
Height (screening only) and weight	X	X			X		X			X
ECGs	X	X	X	X	X		X	X		
Safety Laboratory Tests	X	X			X		X	X		X
[b] Bolus **(OL Bolus-Oral group only)**		X								
PK sample collection			X	X	X	X	X	X		
PK subgroup sample collection		[c] X								
Neurosteroid sample collection		X	X	X	X		X	X		X
Urinalysis, Drug Screen and Pregnancy	X	X		X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X	X	X
[a] HAMD17	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
CGI-S	X	X								
EPDS	X	X	X	X	X	X	X	X	X	X
STAI6	X	X	X	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X	X	X	X
SSS		X	X	X	X	X	X	X	X	X
Start Taper							X			

[a] CTNI will conduct all HAMD ratings except the one at screening

[b] IV bolus is to be done at approximately 4 pm (preferably within ±1 hour) and allowing for at least 1-hour post-bolus follow-up at the site before discharge

[c] A sub-group of 6 subjects (to be called 'PK sub-group') in each of the OL 1,125 mg and OL Bolus-Oral groups will stay overnight on the unit between Day 1 and Day 2 to undergo comprehensive PK assessment as follows: for the OL 1,125 mg group plasma samples for PK analysis will be drawn at the following times after the first oral dose on Day 1 (e.g., the 675 mg oral capsules dose at 7 pm at dinner time; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the 10 pm 675 mg dose), at +4hr, +5hr, +6hr, and at 8 am on Day 2. For the OL Bolus-Oral group plasma samples for PK analyses will be drawn at the following times after the IV bolus on Day 1 (e.g., the 12 mg IV bolus at 4 pm; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the first oral dose of 750 mg oral suspension at dinner time), at +4hr, +5hr, +6hr (i.e., just prior to the second 750 mg oral suspension evening dose), at + 7hr, +8hr, and at 8 am on Day 2.

The following priority order will be in effect when more than 1 assessment is required at a particular time point: 1) HAMD17 2) CGI-I/CGI-S 3) EPDS 4) STAI6 5) SSS 6) CSSRS 7) vital signs 8) ECG 9) safety labs 10) neurosteroid sample 11) PK sample 12) urinalysis, urine drug screen and pregnancy test 13) physical examination. SAFER interview is scheduled if subject meets the eligibility criteria at the Screening visit. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study. Screening period may be extended to 21 days with approval from the medical monitor.

7.10 Study Evaluations and Procedures

7.10.1 Demographics, Medical History, and Other Baseline Characteristics

Demographics, medical history, and other baseline characteristics will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit.

7.10.2 Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the principal investigator or designated study personnel. The purpose of this study will be discussed with the subject.

7.10.3 Eligibility Review

An eligibility review will be conducted by the investigator at the visits specified in Table 8, using the subject inclusion and exclusion criteria as detailed in Section 4.

7.10.4 Prior Medication, Concomitant Medication and Concomitant Therapy Review

At screening, prospective subjects will be asked about medications they have taken in the previous 60 days, including prescription medications, non-prescription medications, herbal medications, vitamins, and supplements. At subsequent visits, the subjects will be asked about medications taken since the last visit.

The medications that were taken within the past 60 days will be recorded. The medications that were taken within the past 60 days but stopped before the screening visit are recorded on the prior medications eCRF page. The medications that were taken during the study period between the screening visit and last follow-up visit, regardless of whether the medication was started during the study period or before the study period, are recorded on the concomitant medications eCRF page.

The following data will be recorded for all medications used by the subject: drug name, dose, regimen, route of administration, start and stop dates, and the indication for use.

The type of psychological counseling the subject received from the time of screening through the last follow-up visit will be recorded on the Concomitant Psychological Treatment eCRF page.

7.10.5 Physical Examination

A complete physical examination will be performed at screening and at Day 10 visit (Day 29 for OL QHS 4 week, OL 1,125 mg and OL Bolus-Oral groups).

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, mouth and throat

- Neck/thyroid/breastfeeding status
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen

The physical examination will be documented in the subject's source documents and on the physical examination eCRF. If a new clinically significant abnormal finding (i.e., not noted at screening) occurs after the screening examination, it must be captured as an AE and documented on the appropriate AE eCRF page.

7.10.5.1 12-lead Electrocardiogram

A 12-lead ECG will be conducted as outlined above. Before each measurement, the subject should be resting in a supine or semi-recumbent position for 10 minutes. RR, PR, QRS, QTcF and QTcB will be collected. ECGs will be measured with equipment calibrated as per the ECG vendors' standard operating procedure. The ECG results will be assessed by a qualified clinician. The investigator's assessment of normal or abnormal will be recorded and entered in the eCRF page. If a new clinically significant abnormal finding (i.e., not noted at Screening) occurs after the Screening examination, it must be captured as an AE or SAE (if it meets criteria for an SAE – see Section 8) and documented on the appropriate AE eCRF page and, if an SAE, submitted to Marinus Safety Department on the SAE form.

7.10.5.2 Clinical Safety Laboratory Evaluations

The name and address of the central clinical laboratory for this study will be maintained in the Investigator's files at each study site.

All clinical laboratory assays will be performed according to the laboratory's normal procedures.

Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the values are clinically significant or not. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

Sodium, potassium, glucose, chloride, carbon dioxide, creatinine, total protein, blood urea nitrogen (BUN), albumin, total bilirubin (with reflex fractionation to direct and indirect bilirubin if total bilirubin is elevated and outside of the normal range), ALT, AST, alkaline phosphatase, thyroid stimulating hormone (with reflex to free T4 if thyroid stimulating hormone (TSH) is

outside of the normal range). The investigator may determine serum β human chorionic gonadotropin (HCG) levels to confirm or exclude pregnancy.

Hematology

Hemoglobin, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, and white blood cell count with differential.

Subjects are not required to be fasting prior to collection of the blood samples.

Urinalysis Including Pregnancy Test and Urine Drug Screen

Leukocytes, nitrites, protein, blood, specific gravity, glucose, ketones, urine pregnancy test, urine drug screen (cannabis, opioids [including oxycodone, methadone and buprenorphine], cocaine, benzodiazepines, barbiturates, alcohol [ethanol], and phencyclidine).

Confirmatory testing of positive drug screen findings using for example gas chromatography mass spectroscopy (GCMS) may be conducted.

7.10.5.3 Adverse Event Collection

Please refer to Section 8, Adverse and Serious Adverse Events Assessment.

7.10.5.4 Vital Signs

Vital signs including BP, pulse, respirations, and temperature (recorded in Celsius [°C]) will be monitored at the time points as outlined above. Vital signs should be collected after the subject has been supine for 5 minutes. If a vital sign measurement is scheduled at the same time as a blood draw, vital signs should be collected prior to the blood draw. Blood pressure should be determined by an appropriately-sized cuff (using the same method, the same arm and in the same position throughout the study). Any abnormal screening vital sign results considered to be clinically significant should be repeated to confirm the finding. Height (in centimeters) will be collected at the screening visit. Weight (in kilograms) will be collected as outlined above.

Any clinically significant deviations from baseline vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.10.6 Interviews, Questionnaires, and Scales

The scales and assessments are listed in Appendix 2. A separate file containing each scale/assessment will be provided to the site.

7.10.6.1 Mini International Neuropsychiatric Interview 7.0

The Mini International Neuropsychiatric Interview (MINI) is a short, clinician-administered, structured diagnostic interview, with an administration time of approximately 15 minutes. The MINI will be administered at the screening visit.

7.10.6.2 The Hamilton Depression Rating Scale

The HAMD is a commonly-used semi-structured clinician-rated instrument which assesses the range of symptoms that are most frequently observed in subjects with major depression. HAMD has undergone a considerable amount of psychometric study and is accepted as a valid standard of symptom outcome assessment in studies of major depression. In this study, the symptoms of depression will be scored using the original 17-item HAMD scale (HAMD17). The 6-item version of this scale, known as HAMD6, will be derived from these data and used as an additional measure of changes in symptoms of depression. The items on the HAMD6 scale are as follows: depressed mood, work and interests, general somatic symptoms (tiredness), anxiety, guilt feelings, and psychomotor retardation. Both HAMD6 and HAMD17 have been validated and used in many clinical trials of antidepressant medications.[11] The use of the 6-item scale is justified because many items on the 17-item version cannot be expected to change over short period of time (e.g. weight).

7.10.6.3 Stanford Sleepiness Scale

Stanford Sleepiness Scale (SSS) is a simple 8-item self-rated scale measuring level of sleepiness the subject is feeling. Level 1 is “feeling active, vital, alert or wide-awake” level 7 is “no longer fighting sleep, sleep onset soon; having dream-like thoughts”; level 8 is sleeping.

7.10.6.4 Clinical Global Impression-Improvement and Clinical Global Impression-Severity

The CGI-I is a 7-point scale that asks the clinician to assess how much the subject's illness has improved or worsened relative to a baseline state at the beginning of the intervention. It is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale that asks the clinician to rate the severity of the subject's depression at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of depression at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

7.10.6.5 Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a 10-question self-rated instrument for assessment symptoms of PPD, such as worry, sleep, mood, and enjoyment. Two questions assessing obsessive thoughts (Obsessive Thoughts Questionnaire) are added to this questionnaire (“How much of your time is occupied by obsessive thoughts over the past 24h?” and “How much distress do your obsessive thoughts cause you?), but they are not included in the calculation of the total EPDS score in the statistical analysis. These 2 questions are rated on a 5-point scale.

7.10.6.6 Spielberg Trait-State Anxiety Inventory, 6 Item Version

The STAI6 is a short questionnaire evaluating anxiety state. The STAI6 has 6 questions, such as “I feel calm,” “I feel tense,” which the subject rates on a scale corresponding to “not at all,” “somewhat,” “moderately”, and “very much.”[12]

7.10.6.7 SAFER Interview

Staff psychiatrists or psychologists at the Massachusetts General Hospital Clinical Trials Network and Institute (CTNI) will perform independent remote SAFER interview (State versus trait; Assessability; Face validity; Ecological Validity; and Rule of 3 Ps (pervasive, persistent, and pathological)) for the screened subjects who are deemed eligible for enrollment to confirm validity of the diagnosis of PPD and eligibility for the study from depression perspective. If the subject was screened by the SAFER team for Marinus study 1042-PPD-2002 and confirmed to have postpartum depression but the HAMD17 severity criteria were not met, the subject could be considered eligible for this study without repeating the SAFER interview provided that the original interview was done within 2 weeks of the screening visit for the current study.

CTNI will also perform all HAMD ratings except the one done at screening.

7.10.6.8 Columbia Suicide Severity Rating Scale (CSSRS)

The CSSRS is a unique, simple, and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality.[13] It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents) that are significantly predictive of completed suicide.

7.10.7 Pharmacokinetic Sampling

Blood samples for pharmacokinetic analysis will be drawn at the times specified in Table 8 to allow determination of ganaxolone plasma levels.

A sub-group of 6 subjects (to be called 'PK sub-group') in each of the OL 1,125 mg and OL Bolus-Oral groups will stay overnight on the unit between Day 1 and Day 2 to undergo comprehensive PK assessment as follows: for the OL 1,125 mg group plasma samples for PK analysis will be drawn at the following times after the first oral dose on Day 1 (i.e., the 675 mg oral capsules dose at 7 pm at dinner time; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the 10 pm 675 mg dose), at +4hr, +5hr, +6hr, and at 8 am on Day 2. For the OL Bolus-Oral group plasma samples for PK analyses will be drawn at the following times after the IV bolus on Day 1 (e.g., the 12 mg IV bolus at 4 pm; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the first oral dose of 750 mg oral suspension at dinner time), at +4hr, +5hr, +6hr (i.e., just prior to the second 750 mg oral suspension evening dose), at + 7hr, +8hr, and at 8 am on Day 2.

The first 6 consecutively enrolled subjects who are in units with overnight inpatient capabilities and who consent for inclusion in the PK subgroup will be included in the PK subgroup.

7.10.8 Neurosteroid Levels

Blood samples for determination of neurosteroid levels (allopregnanolone and potentially other metabolites of progesterone) will be collected at time points specified in Table 8.

7.10.9 Volume of Blood to Be Drawn from Each Subject

Table 9. Volume of Blood to Be Drawn from Each Subject for the OL TID, OL QHS and Double-blind Groups

Assessment	Approximate Sample Volume (mL)[a]	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples	4	5	20
Safety hematology	3	3	9
Safety chemistry	7	3	21
Neurosteroid level	4	2	8
Total mL			58

Table 10. Volume of Blood to Be Drawn from Each Subject for the OL QHS 4 Week, OL 1,125 mg, and OL Bolus-oral groups

Assessment	Approximate Sample Volume (mL)[a]	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples	4	6	24
Safety hematology	3	6	18
Safety chemistry	7	6	42
Neurosteroid level	4	7	28
Total mL			112

Table 11. Volume of Blood to Be Drawn from Each Subject for the PK Subgroup of OL 1,125 mg Group

Assessment	Approximate Sample Volume (mL)[a]	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples	4	12	48
Safety hematology	3	6	18
Safety chemistry	7	6	42
Neurosteroid level	4	7	28
Total mL			136

Table 12. Volume of Blood to Be Drawn from Each Subject for the PK Subgroup of OL Bolus-Oral Group

Assessment	Approximate Sample Volume (mL)[a]	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples	4	14	56
Safety hematology	3	6	18
Safety chemistry	7	6	42
Neurosteroid level	4	7	28
Total mL			144

During this study, approximately 58 mL of blood will be drawn from all subjects during the study for the OL TID, OL QHS and Double-blind groups. Approximately 112 mL of blood will be drawn from all subjects during the study for the OL QHS 4 week, OL 1,125 mg, and OL Bolus-Oral groups.

Subjects in the 'PK subgroup' of the OL 1,125 mg and OL Bolus-oral groups (6 subjects in each subgroup) will have additional 6 and 8 samples, respectively, at 4 mL each, for a total of approximately 136 mL and 144 mL of blood drawn, respectively.

7.10.10 Safety Plan for Medical Emergencies

If the subject exhibits suicidal ideation during the study visit (for example answering "yes" to questions 4 and 5 in the suicidal ideation part of the CSSRS) she must be evaluated by a psychiatrist immediately. Suicidality assessment and the decision regarding further evaluation and treatment may be done by a psychiatrist principal investigator (or a sub-investigator). If a psychiatrist is not available at the study site, the site must have a plan how to access psychiatric care immediately, for example at a local emergency room or other acute care facility.

Each investigative study site must provide 24-hour medical coverage to address questions from the subjects and respond to medical emergencies, such as suicidal ideation and adverse events, including during the off-duty hours. Each subject will be provided with a wallet card and information how to contact the study site at all hours.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Council on Harmonisation [ICH] Guidance E2A 1995).

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since the previous visit/you were last asked?"). All AEs are collected from the time the informed consent is signed until the end of the follow-up period. This includes events occurring during the screening period of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure, regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached (AE has resolved), stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. Any changes in the severity of the AE must be recorded.

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Causality Categorization

The investigator will assess causal relationship between the investigational product and each AE (i.e, their relationship to study drug), and answer "yes" or "no" to the question, "*Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"*

8.1.3 Variables

The following variables will be collected for each AE:

- AE
- The date when the AE started and stopped
- Maximum intensity or intensity or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the study drug (yes or no)
- Action taken with regard to investigational product (none, dose reduced, interrupted, withdrawn)
- AE caused subject's discontinuation from study *(*yes or no*)*
- Outcome (fatal, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, recovered/resolved, unknown)

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study (e.g., depression) should not be classified as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Adverse Events Based on Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a there is a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment period, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "*Have you had any health problems since the previous visit/you were last asked?"* or revealed by observation, will be collected and recorded in the eCRF.

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the end of the follow-up period.

Any report of pregnancy for any study participant must be reported within 24 hours to Marinus Safety Department or its delegate using the Pregnancy Report Form (and any applicable follow-up reports). The study participant must be withdrawn.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Marinus Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Marinus Serious Adverse Event Form to Marinus Safety Department. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the Investigator's Brochure (IB), which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to Marinus Safety Department within 24 hours of the first awareness of the event.

The investigator must complete, sign, and date the Marinus Serious Adverse Event Forms and verify the accuracy of the information recorded on the form with the corresponding source documents and fax or e-mail the form to:

Email: safetyPPD2003@marinuspharma.com

Fax: 484-679-2138

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless they result in an SAE.

8.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- **Results in death**
- **Is life-threatening.** Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization.** Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as an SAE(s).
- **Results in persistent or significant disability/incapacity.**
- **Is a congenital abnormality or birth defect.**
- **Is an important medical event.**

  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the end of the follow-up period and must be reported to the Marinus Safety Department or its delegate within 24 hours of the first awareness of the event. In addition, the Marinus medical monitor should be informed of the event within 24 hours via either email or a phone call.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Marinus Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and IV dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e. the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received the investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or its delegate is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs.

In addition, the sponsor or its delegate is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the ganaxolone clinical development program.

The investigator is responsible for notifying the local Institutional Review Board (IRB), local Ethics Committee (EC), or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRFs. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is enrolled, it is expected that site personnel will complete the eCRF entry within approximately 2 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the eCRF completion guidelines or data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Plan

The SAP will provide the statistical methods and definitions for the analysis of the safety and efficacy data, and it will describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing data will be addressed.

The SAP will be finalized prior to database lock and/or unblinding of any portion of the trial to preserve the integrity of the statistical analysis and study conclusions.

9.3.1 Data Review Committee (DRC) and Recommendations for Dosing

Adverse events and other safety data, including sedation and dosing changes, will be adjudicated by the DRC before proceeding to the double-blind part of the study. The dose recommendation will be made by a DRC comprised of the Marinus Chief Medical Officer and 2 external physicians and potentially other experts familiar with the clinical care of women with major depression or PPD and with experience in conducting clinical trials. The DRC may also consult other experts, such as a statistician and a pharmacokineticist. A separate guidance document will outline the functions and membership of the DRC.

After completion of the double-blind part, the data will be evaluated by an independent DRC. Based on the analysis and recommendation by the DRC, the study may be closed at that point, or

an additional approximately 50 women with PPD will be treated with ganaxolone or placebo under a similar study design but using a different dosing regimen. The daily dose may be lowered, increased, or the previous dosing may be repeated. However, the total daily dose will not exceed 1,200 mg and no single dose will be higher than 675 mg.

Marinus may decide to stop the study, or make the data public at any time during the open-label portion of the trial or after completion of the double-blind part of the study.

9.3.2 Justification for Sample Size

With a sample size of 50 subjects/group, the DBPC part of the trial will be able to detect a medium effect size (per Cohen's d) with 93% power using a two-sided significance level of 0.05.

9.3.3 Study Population

The **Screened Set** will consist of all subjects who have signed an informed consent.

The **Randomized Set** will consist of subjects randomized in the DBPC part of the trial.

The **Safety Set** will consist of all subjects who received IV IP.

The **modified Intent to Treat Set** (mITT) will consist of all subjects in the DBPC part of the trial who received IP and who have at least 1 post-baseline HAMD17 assessment. The mITT set will be the primary efficacy population for the DBPC part of the trial.

The **Per-Protocol Set** will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints.

9.4 Analysis Methods

Data will be presented by study part (OL, DBPC), dosing or treatment group within study part and, if applicable, study visit. Continuous variables will be summarized as numbers of observations, means, measures of variance (e.g., standard deviation), and percentiles (e.g., median, minimum, maximum). Categorical variables will be summarized as numbers of observations and percentages.

9.4.1 Demographic and Baseline Characteristics

Baseline characteristics will include a summary of the following:

- Subject demographics
- Pre-existing medical conditions
- Prior therapies
- Medical history

9.4.2 Subject Disposition

Frequencies and percentages of subjects who discontinued the study and reasons for discontinuation will be summarized.

9.4.3 Investigational Medicinal Product

Overall exposure to investigational product, such as duration of exposure, as well as dose adjustments (i.e., deviations from the scheduled titration scheme) will be summarized.

9.4.4 Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) and will be summarized by drug class and preferred drug name.

9.4.5 Safety Analyses

Reported AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment emergent AEs (TEAEs), defined as AEs that started or worsened after first administration of IP, will be summarized by system organ class and preferred term. Separate summaries of TEAEs by severity and relatedness will be done. SAEs and TEAEs leading to discontinuation of the study drug will also be summarized separately.

The absolute values and change from baseline in laboratory tests, vital signs, SSS, ECG parameters, and CSSRS will be summarized.

Results of physical examinations will be listed.

9.4.6 Efficacy Analyses

Efficacy parameters will be summarized for both the open-label and DBPC parts but will be analyzed only for the DBPC part. For the open-label part, referring to efficacy endpoints as "primary," "secondary," and "exploratory" is related to the degree of influence each type of endpoint is expected to have on decision-making rather than to considerations associated with inferential analysis (such as control of type 1 error). The primary time point of interest for all efficacy parameters will be Day 10 for the DBPC part and the visit at end of treatment (before initiation of taper) for the open-label part.

9.4.6.1 Primary Endpoint

The primary efficacy endpoint will be HAMD17 total score change from baseline; this will be assessed at Day 10 for the DBPC part and at the visit at end of treatment for the open-label part. The primary efficacy analysis will be done using the mITT set (DBPC part only). The analytical method will be mixed model repeated measures (MMRM) with baseline HAMD17 total score as a covariate. Significance will be tested at a two-sided 0.05 level. Unstructured covariance will be specified although alternative covariance structures may be used, if appropriate, to achieve convergence or greater efficiency. Sensitivity analysis will be used to evaluate the assumption of data missing at random (MAR), if applicable.

9.4.6.2 Secondary Endpoints

The trial will also evaluate the following secondary endpoints at each post-baseline data collection time point to provide additional evidence of the efficacy of ganaxolone in treating PPD:

- Change from baseline in HAMD17 total score other than at the primary endpoint time point
- HAMD17 response defined as at least a 50% reduction from baseline in total score
- HAMD17 remission defined as total score <= 7
- Change from baseline in EPDS total score
- Change from baseline in STAI6
- CGI-I

9.4.6.3 Exploratory Endpoints

Several endpoints will be evaluated for signals of efficacy to explore whether any should be elevated in importance in subsequent trials. Change from baseline to each post-baseline data collection time point will be summarized for the following exploratory endpoints:

- HAMD6 (Bech) subscale of HAMD17: depressed mood, feelings of guilt, work and activities, retardation, anxiety psychic, and general somatic symptoms (Items 1, 2, 7, 8, 10, 13)
- Anxiety/Somatization subscale of HAMD17: anxiety psychic, anxiety somatic, somatic symptoms gastro-intestinal, general somatic symptoms, hypochondriasis, and insight (Items 10-13, 15, 17)
- Gibbons Global Depression Severity subscale of HAMD17: depressed mood, feelings of guilt, suicide, work and activities, agitation, anxiety psychic, anxiety somatic, genital symptoms (Items 1-3, 7, 9-11, 14)
- HAMD17 individual items
- Anxiety subscale derived from EPDS Items 3-5 (“I have blamed myself unnecessarily when things went wrong,” “I have been anxious or worried for no good reason,” “I have felt scared or panicky for no very good reason”)
- EPDS individual items

9.4.6.4 Statistical Methods

Efficacy parameters will be summarized for open-label and DBPC parts. Observed values and changes from baseline for HAMD17, EPDS, and STAI6 total scores, subscales, and individual items will be summarized by visit. The categorical outcomes of HAMD17 response, HAMD17 remission, and CGI-I will be summarized by visit.

For the DBPC part, the preferred approach for analyses of treatment group differences in secondary and exploratory continuous efficacy variables will be MMRM but other approaches such as t-tests, analysis of covariance, or non-parametric methods may be used if necessary or more practical. Similarly, the preferred approach for analysis of secondary and exploratory

categorical efficacy variables will be repeated measures (e.g., generalized estimating equations) but other approaches such as chi square or Fisher's exact tests may be used.

9.4.7 Other Analyses

No other analyses are planned in this study.

9.4.8 Handling of Missing and Incomplete Data

While every attempt must be made by the investigator to provide complete data, there are cases in which this may not always be possible (e.g., incomplete subject recall of start and stop dates). Unrecorded values will be treated as missing, except for severity and relationship to investigational medicinal product for AEs. If the severity or relationship to investigational medicinal product is missing for an AE, which occurred post administration of investigational medicinal product, the event will be regarded as severe and related to investigational medicinal product, respectively.

After completion of the study, a set of sensitivity analyses will be conducted to evaluate the impact of missing data on the results. The methodologies for the addressing missing data will be specified in the Statistical Analysis Plan (SAP).

9.4.9 Pharmacokinetic Analyses

Five samples of blood will be collected to determine ganaxolone plasma concentrations during the study. Samples will be collected on 3 occasions during treatment with ganaxolone to determine trough concentrations in plasma. An additional 2 samples of blood will be collected at follow up visits, after ganaxolone treatment has been completed, to monitor the disappearance of ganaxolone following cessation of treatment.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, European Union (EU) Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., contract research organization [CRO]) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current Good Clinical Practice (GCP) and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained personnel are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The primary diagnosis and eligibility for the trial are assessed by a qualified licensed physician investigator (or his/her delegate) at the study site. The physician at the study site will be accountable for clinical assessments, physical examinations, and medication administration (including deciding whether the dose is escalated or not). The remote SAFER interview will be conducted to confirm the diagnosis of PPD and eligibility for the trial from the depression severity point of view.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol. If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Electronic case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all

observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the eCRF. All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, including past psychiatric history.

The investigator must permit authorized representatives of the sponsor, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor will check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for

ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e, a complete set of subject information sheets and fully executed signature pages) must be given to the subject. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

If local IRB/EC is used, the principal investigator provides the sponsor or its delegate with a copy of the consent that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented prior to study start that another party (i.e, CRO or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor or delegate.

10.3.2 Institutional Review Board or Ethics Committee

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor or its delegate has received written IRB/EC approval of and copies of revised documents.

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case, at least once a year. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) act of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor or its delegate.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives may review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor in verifying the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies - containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results and Publication Policy

Marinus will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, public presentations to the investors in the company, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific or company website, or other disclosure of the study results, in printed, electronic, oral or other form. The results may be made public after completion of either the open-label part or double-blind part.

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12 APPENDICES

Appendix 1. Prohibited Strong CYP3A4 Inhibitors and Inducers

Prohibited strong inhibitors	Prohibited strong inducers
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Barbiturates
Clarithromycin	Carbamazepine
Itroconazole	Enzalutamide
Ketoconazole	Glucocorticoids
Nefazadone	Modafinil
Saquinavir	Oxcarbazepine
Suboxone	Phenobarbital
Telithromycin	Phenytoin
Grapefruit juice	Pioglitazone
	Rifabutin
	Rifampin
	St. John's Wort
	Troglitazone

Source: The Flockhart Table (http://medicine.iupui.edu/clinpharm/ddis/main-table)

Appendix 2. Scales and Assessments

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Version
Hamilton Depression Rating Scale (HAMD17)	17-item version
Spielberg Trait-State Anxiety Inventory	6-item version
Edinburgh Postnatal Depression Scale (EPDS)	Two obsession items are added to the standard EPDS questionnaire
Columbia Suicide Severity Rating Scale	Baseline and since last visit (standard)
Stanford Sleepiness Scale	NA
Mini International Neuropsychiatric Assessment	Version 7.0
Clinical Global Impression - Improvement	NA
Clinical Global Impression - Severity	NA

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 3. Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol – Version 1	09 Jun 2017	Global
Amendment 1 – Version 2	15 Aug 2017	Global
Amendment 2 – Version 3	25 Jan 2018	Global
Amendment 3 – Version 4	05 Jun 2018	Global
Amendment 4 – Version 5	22 Oct 2018	Global

Amendment 4 Summary of Changes from version June 5, 2018 to 22 Oct, 2018

<table>
<tr><th>Page</th><th>Section, Title, Paragraph, Line</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>1

13</td><td>Title Page

Study Synopsis Title</td><td>TITLE: A Phase 2, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of Oral Administration of Ganaxolone in Women with Postpartum Depression</td><td>TITLE: A Phase 2, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of IV and Oral Administration of Ganaxolone in Women with Postpartum Depression</td></tr>
<tr><td colspan="4">Reason for Change: Addition of intravenous administration of Ganaxolone to study</td></tr>
<tr><td>1</td><td>Title Page</td><td>
<table>
<tr><th>Document</th><th>Date</th><th>Global/Country/Site Specific</th></tr>
<tr><td>Original Protocol – Version 1</td><td>09 Jun 2017</td><td>Global</td></tr>
<tr><td>Amendment 1 – Version 2</td><td>15 Aug 2017</td><td>Global</td></tr>
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<tr><td>Amendment 4 – Version 5</td><td>22 Oct 2018</td><td>Global</td></tr>
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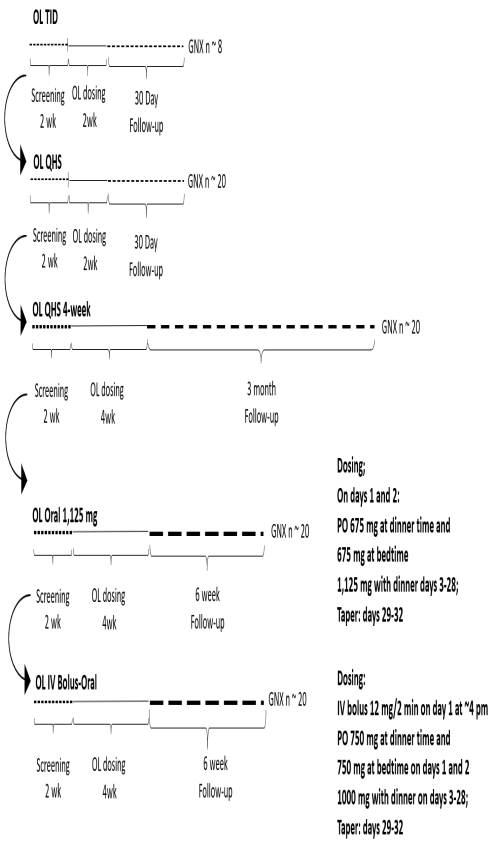
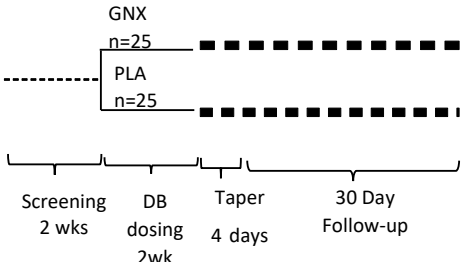
<tr><td colspan="4">Reason for Change: Administrative change – Protocol history added</td></tr>
<tr><td>2</td><td>Protocol Signature Page</td><td>Maciej Gasior, MD, PhD, Executive Director, Clinical Development</td><td>Rolando Gutierrez-Esteinou, MD
Vice President, Clinical Development and Pharmacovigilance</td></tr>
<tr><td colspan="4">Reason for Change: Change to Sponsor Medical Contact and Medical Monitor</td></tr>
</table>

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
3	Sponsor Contacts	Maciej Gasior, MD, PhD Executive Director, Clinical Development Telephone: 484-801-4687 Email: mgasior@marinuspharma.com	**Rolando Gutierrez-Esteinou, MD** **Vice President, Clinical Development and Pharmacovigilance** **Marinus Pharmaceuticals Inc.** **Telephone: : 484-801-4678 | F: 484-801-4669** **Email: rgutierrez@marinuspharma.com**
Reason for Change: Change to Sponsor Medical Contact and Medical Monitor			
13	Study Synopsis	Drug: Ganaxolone oral capsule formulation	Drug: Ganaxolone **IV, oral suspension, and oral capsule formulations**
Reason for Change: Addition of intravenous administration of Ganaxolone to study and clarification of oral formulations			
13	Study Synopsis		**Design:** **This is a Phase 2, multicenter study in women with postpartum depression (PPD) consisting of 2 parts: Open Label Part: multiple ascending dose open-label focused on safety and tolerability in 5 groups that differ by total daily dosing and formulation of study drug; and Double-blind Part is a double-blind placebo-controlled (DBPC) focused on safety, tolerability and efficacy in one group. The Double-blind Part will begin after the Open Label Part dosing is completed. The dosing, treatment duration and timing of evaluations for the double-blind portion of the study will be decided based on the results of the Open Label Part and recommendations of the Data Review Committee (DRC). The DRC is comprised of Marinus' Chief Medical Officer and 2 external physician experts.** **Figures 1A and 1B depict the design for each subject group in the Open Label and Double-blind Parts, respectively.**
Reason for Change: Clarification of study design			
13	Study Synopsis	Number of subjects (total and for each treatment arm): This is a Phase 2, multicenter study in women with postpartum depression (PPD) consisting of 2 dosing groups: an initial open-label safety group and a double-blind placebo-controlled group. The open-label safety group will	Number of subjects **and dose regimen for each treatment arm:** **For Open Label Part, approximately 176 women 18 to 48 years of age with PPD will be screened to enroll**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		be enrolled and dosing completed before proceeding to the double-blind group. The goal of the open-label group is to explore the safety of oral ganaxolone in this population and identify a dosing regimen for the double-blind phase. For the open-label safety group approximately 48 women 18 to 48 years of age with PPD will be screened to enroll approximately 24 patients. During this open-label safety phase, for the first approximately 8 patients, ganaxolone will be titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days. This dosing group is called open-label 3 times daily (OL TID) group. For the next approximately 8 patients, ganaxolone will be administered at bedtime (QHS). For these patients ganaxolone will be titrated to a dose of 675 mg QHS over 4 days, which is then maintained until day 10, followed by a taper over 4 days. This dosing group is called OL QHS group. For the next approximately 8 patients of the open-label safety group, ganaxolone will be administered at a dose 675 mg QHS for 28 days, followed by a taper over 4 days. This dosing group is called OL QHS 4-week dosing group. The investigator has the flexibility to adjust the dose if the patient experiences sedation, dizziness or other untoward effects in each dosing group. For the double-blind group, approximately 100 women with PPD 18 to 48 years of age will be screened to randomize 50 women in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days. The dosing for the double-blind portion of the study will be decided based on the results of the open-label portion and recommendations of the Data Review Committee (DRC). The DRC is comprised of Marinus' Chief Medical Officer and 2 external physician experts. The total daily dose will not exceed 1200 mg. Randomization will be stratified by the use of concomitant antidepressants so that the number of patients who are treated with antidepressants and who are not treated with antidepressants	**approximately 88 subjects.** **The first group (called OL TID) of approximately 8 subjects will receive oral ganaxolone (capsules) titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days.** **The second group (called OL QHS) of approximately 20 subjects will receive oral ganaxolone (capsules) at bedtime (QHS), titrated to a dose of 675 mg QHS over 4 days, which is then maintained until day 10, followed by a taper over 4 days.** **The third group (called OL QHS 4-week) of approximately 20 subjects, oral ganaxolone (capsules) will be administered at a dose of 675 mg QHS for 28 days, followed by a taper over 4 days.** **The fourth group (called OL 1,125 mg group) of approximately 20 subjects will receive, on the first 2 days, oral ganaxolone capsules at a dose of 675 mg at approximately 7 pm (with dinner) and 675 mg at 10 pm; followed, by 26 days of ganaxolone 1,125 mg at dinner time; followed by a taper over 4 days. Approximately 6 subjects will participate in PK collection that requires an overnight stay on Day 1.** **The fifth group (called OL Bolus-Oral) of approximately 20 subjects will receive ganaxolone starting with a single IV bolus 12 mg over 2 minutes at approximately 4 pm of Day 1; followed by ganaxolone oral suspension 750 mg at 6pm (with a fatty meal) and 750 mg at 10pm. On Day 2 subjects will receive ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime, followed by 26 days of ganaxolone oral suspension 1,000 mg at dinner time, Treatment will be tapered over 4 days. Approximately 6 subjects will participate in PK collection that requires an overnight stay on Day 1.**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		will be similar in each treatment group.	**FIGURE 1A: Design of Open-Label Part**  For the double-blind placebo-controlled (DBPC) part, approximately 100 women with PPD 18 to 48 years of age will be screened to randomize 50 women in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days. The dosing, treatment duration and timing of evaluations for the double-blind portion of the study will be decided based on the results of the Open Label Part and recommendations of the Data Review Committee (DRC). The total daily dose will not exceed 1,600 mg. Randomization will be stratified by the use of concomitant

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
			antidepressants so that the number of subjects who are treated with antidepressants and who are not treated with antidepressants will be similar in each treatment group. **FIGURE 1B: Design of the Double-Blind Placebo-Controlled Part**  The investigator has the flexibility to adjust the dose and/or timing of the dose if the subject experiences sedation, dizziness or other untoward effects in each dosing group, by reducing the dose first to a lower level and possibly increasing it back again later if tolerance develops to the untoward effects (see section 6.2.7).
Reason for change: Clarification of number of subjects and dose regimen for each treatment arm			
15	Study Synopsis	Objectives: Open-label safety group:	Objectives: **Open-label Part: Safety, dosing, efficacy and pharmacokinetics:** **3. To assess the efficacy of ganaxolone using the Hamilton Depression Rating Scale 17-item version (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory 6-item version (STAI6) and Clinical Global Impression-Severity and Improvement (CGI-S and CGI-I) scales.** **4. To collect samples of blood for pharmacokinetic (PK) analysis after administration of oral and IV ganaxolone to use in population-pharmacokinetics analyses, the results of which will be reported separately by the Sponsor.**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		Double-blind phase: The primary efficacy variable in this study is change from baseline in the HAMD17 total score on Day 10 between ganaxolone and matching placebo.	**Double-Blind placebo controlled (DBPC) Part: Safety, efficacy, and pharmacokinetics:** The primary efficacy variable in this study is change from baseline in the HAMD17 total score on Day 10 **of the DBPC part** between ganaxolone and matching placebo.
Reason for change: Clarification of study objectives			
15	Study synopsis	Investigational product, dose, and mode of administration: Ganaxolone oral capsule (225 mg/capsule) formulations and matching placebo will be used.	Investigational product, dose, and mode of administration: **Ganaxolone IV, oral suspension, and** oral capsule (225 mg/capsule) formulations and matching placebo will be used.
Reason for Change: Addition of intravenous administration of Ganaxolone to study and clarification of oral formulations			
15	Study synopsis 4.1 – Inclusion criteria	6. HAMD17 score of ≥ 20 but < 26 at screening 7. HAMD17 ≥ 18 at the time of randomization (Day 1)	6. HAMD17 score of ≥ 20 **at screening rated by a certified site rater** 7. HAMD17 ≥ 18 **on Day 1 prior to study drug administration**
Reason for change: Clarification of exclusion criteria			
16	Study synopsis	Maximum duration of subject involvement in the study**:** Approximately 7 weeks for the OL TID and OL QHS groups and the double-blind phase. The duration for the OL QHS 4 week group is approximately 18 weeks.	Maximum duration of subject involvement in the study**:** Approximately 7 weeks for the OL TID and OL QHS groups and the **DBPC part**. The duration for the OL QHS 4-week group is approximately 18 weeks **and the duration for the OL 1,125 mg and OL Bolus-oral groups is approximately 12 weeks.**
Reason for change: Addition of 2 treatment groups			
16	Study synopsis	Key variables: Safety: Adverse events, vital signs, CSSRS, ECG, SSS, and physical examination. Efficacy: Hamilton Depression Rating Scale (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory 6 item version (STAI6) and	Key variables: Safety: Adverse events, **laboratory measures,** vital signs, CSSRS, ECG, SSS, and physical examination. Efficacy: HAMD17, EPDS, STAI6, CGI-I and **CGI-S scales**.

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		Clinical Global Impression-Improvement (CGI-I) scale. Pharmacokinetics**:** For the OL TID and OL QHS groups a total of five samples of blood will be collected to determine ganaxolone plasma concentrations during the study. Samples will be collected on 3 occasions during treatment with ganaxolone to determine trough concentrations in plasma. An additional 2 samples of blood will be collected at follow up visits, after ganaxolone treatment has been completed, to monitor the disappearance of ganaxolone following cessation of treatment. For the OL QHS 4-week group seven samples of blood will be collected to determine ganaxolone plasma concentrations during the study. Samples will be collected on 5 occasions during treatment with ganaxolone to determine trough concentrations in plasma. Two additional samples of blood will be collected at the first two follow up visits, after ganaxolone treatment has been completed, to monitor the disappearance of ganaxolone following cessation of treatment. Statistical Methods: Approximately continuous endpoints will be analyzed using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) with fixed factors of treatment, visit, the treatment-by-visit interaction, and baseline value of the endpoint. Ordered categorical endpoints will be analyzed at each visit by the Cochran-Mantel-Haenszel (CMH) row mean scores test using rank scores. Dichotomous categorical endpoints will be analyzed at each visit by Fisher's exact test.	Pharmacokinetics**:** For the OL TID and OL QHS groups, a total of 5 samples of blood will be collected to determine ganaxolone plasma concentrations during the study. Samples will be collected on 3 occasions during treatment with ganaxolone to determine trough concentrations in plasma. An additional 2 samples of blood will be collected at follow up visits, after ganaxolone treatment has been completed, to monitor the disappearance of ganaxolone following cessation of treatment. For the OL QHS 4-week, **OL 1,125 mg, and OL Bolus-oral groups, 6 samples** of blood will be collected to determine ganaxolone plasma concentrations during the study. Samples will be collected **on 4 occasions during treatment in the OL QHS 4 weeks group and on** 5 occasions during treatment in the **OL 1,125 mg and OL Bolus-oral** groups to determine **ganaxolone** trough concentrations in plasma. Two additional samples of blood will be collected in the first 2 follow up visits **in the OL QHS 4 weeks group and 1 additional sample will be collected in the OL 1,125 mg, and OL Bolus-oral groups at the first follow up visit** after ganaxolone treatment has been completed, to monitor the disappearance of ganaxolone following cessation of treatment. **Statistical Methods: Data will be presented by study part (OL, DBPC), dosing or treatment group within study parts and if applicable, study visit. Continuous variables will be summarized as numbers of observations, means, measures of variance (e.g., standard deviation), and percentiles (e.g., median, minimum, maximum). Categorical variables will be summarized as numbers of observations and percentages.** **<u>Analysis Populations</u>: The Screened Set will consist of all subjects who have signed an informed consent. The Randomized Set will consist of subjects randomized in the DBPC part of the trial. The Safety Set will consist of all subjects who received investigational product (IP). The modified Intent to Treat (mITT) Set will consist of all subjects in the DBPC part of the trial who received IP, and**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
			who have at least 1 post-baseline HAMD17 assessment. The Per-Protocol Set will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints. **Efficacy Analysis: Efficacy parameters will be summarized for both the OL and DBPC parts, but will be analyzed only for the DBPC part. The primary time point of interest for all efficacy parameters will be Day 10 for the DBPC part and the visit at end of treatment (before initiation of taper) for the OL part. The primary efficacy endpoint will be change from baseline in HAMD17 total score at Day 10 for the DBPC part and at the visit at end of treatment for the OL part. The primary efficacy analysis will be done using the mITT set (DBPC group only), and the analytical method will be** mixed model repeated measures (MMRM) with **baseline HAMD17 total score as a covariate. Significance will be tested at a two-sided 0.05 level.** **Secondary efficacy** endpoints will be **change from baseline in HAMD17 total score other than at the primary endpoint time point, HAMD17 response defined as at least a 50% reduction from baseline in total score, HAMD17 remission defined as total score < = 7, change from baseline in EPDS total score, change from baseline in STAI6, and CGI-Improvement. HAMD17 and EPDS individual items as well as several HAMD17 subscales will be considered exploratory.**
Reason for change: Clarification and addition of key study variables			
22	2.2.1. Objectives of the Open-label Safety Part		**2.2.1.3 Efficacy Objective** **To assess the efficacy of ganaxolone using the Hamilton Depression Rating Scale 17-item version (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory 6-item version (STAI6) and Clinical Global Impression-Severity and Improvement (CGI-S and CGI-I) scales.** **2.2.1.4 Pharmacokinetic Objective**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
			To collect samples of blood for pharmacokinetic (PK) analysis after administration of oral and IV ganaxolone to use in population-pharmacokinetics analyses, the results of which will be reported separately by the Sponsor.
Reason for Change: Addition of efficacy and pharmacokinetic objectives in the Open-label Safety Part			
24	3.1. Study Design and Study Population	For the open-label safety group approximately 48 women 18 to 48 years of age with PPD will be screened to enroll approximately 24 patients. During this open-label safety phase, for the first approximately 8 patients, ganaxolone will be titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days. This dosing group is called OL TID group. For the next approximately 8 patients of the open-label safety group, ganaxolone will be administered at bedtime (QHS). For these patients ganaxolone will be titrated to a QHS dose of 675 mg over 4 days which is then maintained until day 10, followed by a taper over 4 days. This dosing group is called OL QHS group	**The investigator has the flexibility to adjust the dose amount and/or timing of dosing if the subject experiences untoward effects during the OL part, by reducing the dose first to a lower level and possibly increasing it back again later if tolerance to the untoward effects develops.** **The open-label safety part will be enrolled, and dosing completed before proceeding to the double-blind part. The goal of the open-label part is to explore safety of IV and oral ganaxolone in this population and identify a dosing regimen for the double-blind part.** **Open-label Part** For the open-label safety **part,** approximately **172** women 18 to 48 years of age with PPD will be screened to enroll approximately **88 subjects.** **In the first group with** approximately 8 **subjects**, ganaxolone will be titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days. This dosing group is called OL TID group. **The second group with** approximately **20 subjects will receive** ganaxolone administered at bedtime (QHS). For these **subjects**, ganaxolone will be titrated to a QHS dose of 675 mg over 4 days which is then maintained until day 10, followed by a taper over 4 days. This dosing group is called OL QHS group **The third group with** approximately **20 subjects will receive** ganaxolone administered at a dose 675 mg QHS for 28 days, followed by a taper over 4 days. This dosing group is called OL QHS 4-week dosing group. **The fourth group with approximately 20 subjects will**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		For the next approximately 8 patients of the open-label safety group, ganaxolone will be administered at a dose 675 mg QHS for 28 days, followed by a taper over 4 days. This dosing group is called OL QHS 4-week dosing group. The investigator has the flexibility to adjust the dose if the patient experiences sedation, dizziness or other untoward effects during the OL phase. The open-label safety group will be enrolled, and dosing completed before proceeding to the double-blind group. The goal of the open-label group is to explore safety of oral ganaxolone in this population and identify a dosing regimen for the double-blind phase.	**receive on the first 2 days ganaxolone capsules 675 mg at dinner time and 675 mg at bedtime (for a total of 1,350 mg per day on the first 2 days) followed by 26 days of ganaxolone capsules 1,125 mg at dinner time, followed by a taper over 4 days. This dosing group is called OL 1,125 mg group.** **The fifth group with approximately 20 subjects will receive ganaxolone as IV bolus 12 mg over 2 minutes at approximately 4 pm of the first day followed by ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime for a total of 1,512 mg on Day 1. On Day 2, subjects will receive ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime, for a total of 1,500 mg, followed by 26 days of ganaxolone oral suspension 1,000 mg at dinner time, followed by a taper over 4 days. This dosing group is called OL Bolus-oral group**
Reason for Change: Clarification of study design and addition of 2 treatment groups			
25	3.2. Rationale for Study Design	This study is intended to test whether ganaxolone is efficacious and safe in treatment of PPD.	**Various dose amounts, formulations, dosing schemes and treatment durations will be evaluated in the Open Label Part to inform the choice of the treatment scheme for the DBPC Part.** **Approximately 8 or 20 subjects, depending of the group, will receive open label ganaxolone to evaluate safety, tolerability, kinetics and efficacy of the drug in women diagnosed with PPD. Assessments of adverse events, laboratory and ECG, and clinical ratings for safety and efficacy will be gathered to evaluate the possible differential effect of the various dosing schemes.** **A double-blind evaluation of safety and efficacy will follow the completion of the open label groups. This study part will utilize a randomized, parallel-group, placebo-controlled design in women diagnosed with PPD. Evaluations of safety and tolerability, as well as efficacy will utilize the same evaluation methods as in the open label part. The primary efficacy endpoint will be change from baseline in HAMD-17 of active vs placebo treatments. The concomitant use of antidepressants or no use of antidepressants will be stratified 1:1 to enroll similar numbers of subjects in each**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
			stratum for both ganaxolone and placebo treatment groups.
Reason for Change: Clarification of the rationale for the study design			
26	3.3. Dose Selection	Open-label QHS dosing group Approximately 8 patients will be allocated to the OL QHS group. The enrollment for the OL QHS group will start after all patients allocated to the OL TID group have started their dosing. Open-label QHS 4-week dosing group Approximately 8 patients will be allocated to the OL QHS 4-week dosing group. The enrollment for the OL QHS 4-week group will start after all patients allocated to the OL QHS group have started their dosing.	Open-label QHS dosing group Approximately **20 subjects** will be allocated to the OL QHS group. The enrollment for the OL QHS group will start after all **subjects** allocated to the OL TID group have started their dosing. Open-label QHS 4-week dosing group Approximately **20 subjects** will be allocated to the OL QHS 4-week dosing group. The enrollment for the OL QHS 4-week group will start after all **subjects** allocated to the OL QHS group have started their dosing. **Open-label 1,125 mg dosing group** **The OL 1,125 mg dosing group is included in the open-label part to explore whether administering ganaxolone orally at doses up to 1,125 mg per day over 4 weeks (including 1,350 in the first 2 days) are safe and well-tolerated and show sustained effects, and whether the therapeutic effects are maintained over a 6-week follow-up period.** **The two evening 675 mg oral doses, within 3 hours of each other on Day 1 are expected to provide mean C_{max} plasma concentrations of approximately 250-300 ng/mL, which may be mildly sedating. Day 2 twin evening dosing is expected to lead to similar exposure. In previous studies ganaxolone has been given up to a daily dose of 2000 mg, and at single doses of 1000 mg. Based on the previous experience this dose is expected to be safe.** **Approximately 20 subjects will be allocated to the OL 1,125 mg dosing group. The enrollment for the OL 1,125 mg group will start after all subjects allocated to the OL QHS 4-week group have started their dosing.** **Open-label Bolus-Oral dosing group**

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			The OL Bolus-Oral dosing group will explore whether administering ganaxolone IV bolus 12 mg followed by oral suspension dosing of up to 1,000 mg per day (including up to 1,500 mg in the first 2 days) is safe and well-tolerated and shows sustained therapeutic effect over 4-weeks of dosing, and whether the therapeutic effects are maintained over a 6-week follow-up period. **This initial bolus infusion is targeted to provide a fast onset of antidepressant activity by delivery of rapid plasma exposures to ganaxolone. Together with the two evening 750 mg oral doses, within 3 hours of each other, Day 1 dosing is expected to provide mean C_{max} plasma concentrations of approximately 250-300 ng/mL, which may be mildly sedating. Day 2 twin evening dosing is expected to lead to similar exposure. In previous studies ganaxolone has been given up to a daily dose of 2,000 mg, and at single doses of 1,000 mg. Based on the previous experience this dose is expected to be safe.** **Approximately 20 subjects will be allocated to the OL Bolus-Oral dosing group. The enrollment for the OL Bolus-Oral group will start after all subjects allocated to the OL 1,125 mg group have started their dosing.** **Dose justification in context of previous experience with IV ganaxolone** **In Study 1042-0405, which was a Phase 1 study in healthy volunteers investigating the safety of IV ganaxolone, the highest bolus dose tested was 30 mg, which was infused over 5-minutes (the same rate, 6 mg/min., as in the OL Bolus-Oral group). This dose led to peak concentration levels (C_{max}) of > 1,000 ng/mL with no safety concerns (except sedation). This safety profile is consistent with findings from previous studies with the oral formulation of ganaxolone, in which C_{max} levels of up to 200 to 300 ng/mL were commonly observed and were not associated with major safety findings or toxicity (apart from sedation-related effects).** Double-blind **Placebo-controlled (DBPC) Part**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		Double-blind phase	**Blinding Scheme** **Subjects will be randomized to ganaxolone or placebo in a 1:1 ratio. The randomization scheme will be prepared by an independent third-party vendor. Treatment assignments will be obtained by the investigator (or designee) via an Interactive Voice and/or Web Response System (IxRS). The placebo infusion and placebo capsules are identical to the ganaxolone infusion and capsules, respectively, in their appearance. An unblinded study pharmacist at the investigative site will prepare the ganaxolone and placebo IV solutions and allocate capsule supply for the double-blind part. Members of the DRC will be unblinded. All other study personnel, including persons involved in the evaluation of the study subjects (e.g. investigators, sub-investigators, and physicians/nurses), with the exception of the study pharmacist, will remain blinded at all times, except in case of an emergency. Subjects will be blinded.**
Reason for Change: Clarification of dose selection, update to number of subjects per treatment group and addition of 2 treatment groups and blinding scheme			
28	3.4. Study Duration	For both the open-label safety OL TID and OL QHS groups, and the double-blind phase of the study the screening period will be up to 2 weeks, followed by a 14-day outpatient treatment period and a 14-day follow-up period. For the OL QHS 4-week dosing group the screening period will be up to 2 weeks, followed by a 28-day outpatient treatment period, a 4-day taper and a 3 month follow-up period.	For both the open-label safety OL TID and OL QHS groups, and the double-blind **part** of the study, the screening period will be up to 2 weeks, followed by a 14-day outpatient treatment period and a 14-day follow-up period. For the OL QHS 4-week dosing group, the screening period will be up to 2 weeks, followed by a 28-day outpatient treatment period, a 4-day taper and a 3-month follow-up period. **For the OL 1,125 mg and OL Bolus-Oral dosing groups, a screening period of up to 2 weeks will be followed by a 28-day outpatient treatment period, a 4-day taper, and a 6-week follow-up period (from Day 29).**
Reason for Change: Addition of study duration for additional treatment groups			

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29	3.6. Definition of Completion		**A dosing group is considered complete when the final subject in the group has completed the final protocol-defined assessment, including follow-up visits, for the group.**
Reason for Change: Addition of the definition of completion			
32	4.4. Discontinuation of Subjects	A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from the investigational product with the medical monitor when possible. If the investigational product is discontinued, regardless of the reason, the evaluations listed for Day 10 for OL TID and OL QHS groups or Day 28 for the OL QHS 4-week group are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-ups. Comments (spontaneous or elicited), complaints, or AEs reported by the subject must be recorded in the source documents. The reason for discontinuation and the date and time of discontinuation of the investigational product must be recorded in the electronic case report form (eCRF) and source documents.	A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from the investigational product with the medical monitor when possible. **Withdrawn subjects who have not received IP will be replaced.** If the investigational product is discontinued, regardless of the reason, the evaluations listed for Day 10 for OL TID and OL QHS groups or **Day 29** for the OL QHS 4-week, **OL 1,125 mg, and OL Bolus-Oral groups** are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-ups. Comments (spontaneous or elicited), complaints, or AEs reported by the subject must be recorded in the source documents. The reason for discontinuation and the date and time of discontinuation of the investigational product must be recorded in the electronic case report form (eCRF) and source documents.
Reason for Change: Clarification of study discontinuation procedure and addition of 2 treatment groups			
34	5.3 - Concomitant Psychological Treatment	Concomitant psychological treatment refers to all psychological care the subject is receiving at the time of the screening visit. Concomitant psychological treatment information must be recorded on the concomitant psychological treatments eCRF page.	Concomitant psychological treatment refers to all psychological care the **subject received from** the time of the screening visit **through the end of the follow-up period.** Concomitant psychological treatment information must be recorded on the concomitant psychological treatments eCRF page.
Reason for Change: Clarification of period of concomitant psychological treatment			

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34	5.3.1.1 – Permitted Psychological Treatments	The subject may continue their current form of psychological treatment (e.g, cognitive behavioral therapy, psychodynamic psychotherapy, supportive psychotherapy) throughout the treatment period. Initiation of a new therapy (a new treatment modality or switching a therapist) is prohibited during the treatment period. After the treatment period, psychotherapy should be continued using the same modality and at the same frequency as during the treatment period, provided that this is medically justified, in order to be able to determine whether there are sustained effects from the treatment the over the 30-day follow-up period. Any changes must be recorded on the concomitant psychological treatments eCRF page.	The subject may continue their current form of psychological treatment (e.g., cognitive behavioral therapy, psychodynamic psychotherapy, supportive psychotherapy) throughout the treatment period. Initiation of a new therapy (a new treatment modality or switching a therapist) is prohibited during the treatment period. After the treatment period, psychotherapy should be continued using the same modality and at the same frequency as during the treatment period, provided that this is medically justified, in order to be able to determine whether there are sustained effects from the treatment the over the **30-, 42-, or 90-day** follow-up periods. Any changes must be recorded on the concomitant psychological treatments eCRF page.
Reason for Change: Clarification of periods for permitted psychological treatments			
37	6.1.2 – Ganaxolone IV Infusion Solution		Manufacturer: Particle Sciences Inc. Vehicle: Captisol® containing sterile IV solution Formulation: IV Strength: 3 mg/ml solution in a glass vial, which is to be diluted with 0.9% saline for the infusion. For details regarding preparation of the infusion solution, please see pharmacy manual. Route of administration: IV
Reason for Change: Addition of identity of intravenous Ganaxolone infusion solution			
37	6.1.3 – Ganaxolone Oral Suspension		Manufacturer: Catalent Pharma Solutions, Somerset, NJ 08873 USA Vehicle: The oral suspension contains ganaxolone (50 mg/mL), hydroxypropyl methylcellulose, polyvinyl alcohol, sodium lauryl sulfate, simethicone, methylparaben, propylparaben, sodium benzoate, citric acid, and sodium citrate at pH 3.8 to 4.2, and is sweetened with sucralose and flavored with artificial cherry. Formulation: Oral suspension Strength: 50 mg/mL oral suspension; 110 mL in 125 mL high-density polyethylene bottles
Reason for Change: Addition of identity of Ganaxolone oral suspension			

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38	6.2 – Administration of Investigational Product(s)	All study medication will be stored at the research pharmacy prior to dispensing, or in a locked cabinet accessible only to members of the investigational research team. Study medication oral capsules) should be stored at room temperature 15°C to 25°C (59°F to 77°F). Ganaxolone will be administered orally with food (breakfast, lunch, dinner, or snack). Ganaxolone should be taken just before or together with a meal or snack and with 240 mL (8 oz) of water.	All study medication will be stored at the research pharmacy prior to dispensing, or in a locked cabinet accessible only to members of the investigational research team. **Ganaxolone** capsules **and ganaxolone oral suspension** should be stored at room temperature 15°C to 25°C (59°F to 77°F). **Ganaxolone stock solution investigational product for IV administration will be stored at refrigerated temperature 2ºC to 8ºC (36ºF to 46ºF). Oral IP should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado), and with 240 mL (8 oz) of water**. **For the IV bolus, ganaxolone 12 mg in 24 mL will be administered over 2 minutes via an indwelling catheter, or a butterfly, inserted in a vein on the arm or hand. The IP should be given as continuous infusion as instructed. The catheter should be flushed with saline at the end of the bolus infusion. For details please see pharmacy manual.**
Reason for Change: Clarification of storage of oral formulations and addition of storage and administration of intravenous ganaxolone			
38	6.2.1 – Allocation of Subjects to Treatment	In the open-label phase the first approximately 8 patients will be assigned to OL TID dosing group. After approximately 8 patients have started dosing in the OL TID group the dosing for the OL QHS group will commence. Approximately eight patients will be dosed for the OL QHS group. After approximately 8 patients have started dosing in the OL QHS group, the enrollment into the OL QHS 4-week group will commence.	In the open-label **part**, the first approximately 8 **subjects** will be assigned to OL TID dosing group. After approximately 8 **subjects** have started dosing in the OL TID group the dosing for the OL QHS group will commence. Approximately **20 subjects** will be dosed for the OL QHS group. After approximately 20 subjects have started dosing in the OL QHS group, the enrollment into the OL QHS 4-week group will commence. **After approximately 20 subjects have started dosing in the OL QHS 4-week group, enrollment into the OL 1,125 mg group will commence. Approximately 20 subjects will be dosed for the OL 1,125 mg group. After approximately 20 subjects have started dosing in the OL 1,125 mg group, enrollment into the OL Bolus-Oral group will commence. Approximately 20 subjects will be dosed for the OL Bolus-Oral group**.
Reason for Change: Update of subject numbers in treatment groups and addition of 2 treatment groups to study			

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<tr><th>Page</th><th>Section, Title, Paragraph, Line</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>45</td><td>6.2.5 – Dosing for the Open-label Treatment Part – OL 1,125 mg Group</td><td></td><td>Subjects will start taking ganaxolone capsules, 675 mg (3 capsules) at dinner time (7 pm) followed by 675 mg (3 capsules) at bedtime (HS) on Day 1 and Day 2 followed by 1,125 mg (5 capsules) at dinner time (7 pm) on the next 26 days (Day 3 through Day 28). A 4-day taper will follow: 900 mg (4 capsules) on Day 29, 675 mg (3 capsules) on Day 30, 450 mg (2 capsules) on Day 31, and 225 mg (1 capsule) on Day 32 (Table 4) all at dinner time.
In addition to screening, there will be study visits on days 1, 2, 8, 15, 22, 29, 36, 57, 71.
Day 29 is the final visit before taper is started. The visit should occur in the morning of Day 29 before noon.
All doses taken must be recorded in the eCRF.
The study visits are intended to allow evaluation of the subject by the principal investigator and making dose and/or timing adjustments when necessary (see Section 6.2.7). If there have been no adverse events the investigator should follow the dosing schedule.
Oral ganaxolone should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado) and with 240 mL (8 oz) of water.

Table 4. Study Drug Dosing Schedule – Open-label 1,125 mg Group
<table>
<tr><th>Visit</th><th>V2</th><th>V3</th><th></th><th>V4</th><th>V5</th><th>V6</th><th>V7</th><th></th><th></th><th></th></tr>
<tr><th>Day</th><th>1</th><th>2</th><th>3</th><th>8</th><th>15</th><th>22</th><th>29</th><th>30</th><th>31</th><th>32</th></tr>
<tr><td>Q7PM</td><td>675 mg</td><td>675 mg</td><td>1,125 mg</td><td>1,125 mg</td><td>1,125 mg</td><td>1,125 mg</td><td>900 mg</td><td>675 mg</td><td>450 mg</td><td>225 mg</td></tr>
<tr><td>QHS</td><td>675 m</td><td>675</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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Page	Section, Title, Paragraph, Line	Original Text	Revised Text
			g m g **Total** 1,350 mg 1,350 mg 1,125 mg 1,125 mg 1,125 mg 1,125 mg 900 mg 675 mg 450 mg 225 mg **There will be total of 10 study visits for the OL 1,125 mg dosing group: Screening, Day 1, Day 2, Day 8, Day 15, Day 22, Day 29 and 3 safety follow-up visits on Day 36, Day 57, and Day 71.**
Reason for Change: Addition of dosing information for OL 1,125 mg Group			
46	6.2.6 – Dosing for the Open-label Treatment Part – OL Bolus-Oral mg Group		Dosing in the Bolus-Oral group will start with ganaxolone IV bolus 12 mg over 2 minutes at approximately 4 pm on Day 1. Subjects will start taking ganaxolone 750 mg oral suspension (15 mL at 50 mg per mL) at dinner time (7 pm) followed by 750 mg oral suspension at bedtime (HS) on Day 1. On Day 2, subjects will again take 750 mg oral suspension at dinner time (7 pm) followed by 750 mg at bedtime (HS). For the following 26 days (Day 3 through Day 28), subjects will take ganaxolone 1,000 mg oral suspension (20 mL at 50 mg per mL) at dinner time (7 pm). A 4-day taper will follow: 750 mg (15 mL) on Day 29, 500 mg (10 mL) on Day 30, 500 mg (10 mL) on Day 31, and 250 mg (5 mL) on Day 32 (Table 5) all at dinner time. In addition to screening, there will be study visits on days 1, 2, 8, 15, 22, 29, 36, 57, 71. Day 29 is the final visit before taper is started. The visit should occur in the morning of Day 29 before noon. All doses taken must be recorded in the eCRF. The study visits are intended to allow evaluation of the subject by the principal investigator and making dose and/or timing adjustments when necessary (see Section 6.2.7). If there have

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been no adverse events the investigator should follow the dosing schedule.

Oral ganaxolone should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado) and with 240 mL (8 oz) of water.

Table 5. Study Drug Dosing Schedule – Open-label Bolus-oral Group

Visit	**V2**	**V3**		**V4**	**V5**	**V6**	**V7**			
Day	**1**	**2**	**3**	**8**	**15**	**22**	**29**	**30**	**31**	**32**
4PM	12 mg IV Bolus									
Q7PM	750 mg	750 mg	1,000 mg	1,000 mg	1,000 mg	1,000 mg	750 mg	500 mg	500 mg	250 mg
QHS	750 mg	750 mg								
Total	1,512 mg	1,500 mg	1,000 mg	1,000 mg	1,000 mg	1,000 mg	750 mg	500 mg	500 mg	250 mg

There will be a total of 10 study visits for the OL Bolus-Oral

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
			dosing group: Screening, Day 1, Day 2, Day 8, Day 15, Day 22, Day 29 and 3 safety follow-up visits on Day 36, Day 57, and Day 71.
Reason for Change: Addition of dosing information for OL Bolus-oral Group			
47	6.2.7 – Dose Adjustments During Open-label		**<u>Adjusting dose and/or timings for the OL 1,125 mg dosing group</u>** **The investigator has the flexibility to adjust dose by reducing the dose to 450 mg (2 capsules) at the second of Day 1 doses (at HS) and/or at either of Day 2 doses, and/or reduce to 900 mg, 675 mg, or 450 mg on Day 3 through Day 28 (at dinner time) if subject experiences sedation, dizziness or other untoward effects during the OL part. The investigator can also change the timing of the evening dose bringing it closer to bedtime and taking it with a fatty snack instead of dinner. Any further adjustments as well as adjusted taper period doses should be discussed with the medical monitor. The investigator may increase the dose back to default levels if tolerance develops to the untoward effects.** **<u>Adjusting dose and/or timings for the OL Bolus-Oral dosing group</u>** **The investigator has the flexibility to adjust dose by reducing the dose to 500 mg (10 mL) for the second of Day 1 doses (at HS) and/or either of Day 2 doses, and/or reduce to 750 mg (15 mL), or 500 mg (10 mL) at dinner time on Day 3 through Day 28 if subject experiences sedation, dizziness or other untoward effects during the OL part. The investigator can also change the timing of the evening dose bringing it closer to bedtime and taking it with a fatty snack instead of dinner. Any further adjustments as well as adjusted taper period doses should be discussed with the medical monitor. The investigator may increase the dose back to default levels if tolerance develops to the untoward effects.**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
Reason for Change: Addition of dose adjustment information for the 2 new treatment groups			
48	6.3.2 – Packaging and Dispensing the Study Drug	Detailed instructions when to take the medication and a reminder to take the study medication with food (just before or with a meal or snack) and with 240 mL (8 oz) of water will be provided to the patient.	Detailed instructions **on** when to take the medication and a reminder to take **oral** study medication **within ±15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado)** and with 240 mL (8 oz) of water, will be provided to the **subject**.
Reason for Change: Clarification of instructions for taking the study drug			
49	6.3.3 – Storage	The 0.3 micron ganaxolone capsules (225 mg) and matching placebos are stored in HDPE bottles with a foil induction seal and child resistant closure at room temperature (15°C to 25°C).	**The ganaxolone stock solution investigational product for the IV administration will be stored at refrigerated temperature 2ºC to 8ºC (36ºF to 46ºF).** The 0.3-micron ganaxolone capsules (225 mg), **oral suspension,** and matching placebos are stored in HDPE bottles with a foil induction seal and child resistant closure at room temperature (15°C to 25°C; **60ºF to 75ºF**).
Reason for Change: Addition of storage instructions for IV Ganaxolone			
50	6.5 – Drug Administration	Oral doses of ganaxolone should be taken with food just before or with a meal or snack and with 240 mL (8 oz) of water at home. The patient must have a reliable family member, significant other or a trusted friend who can take the role for being the primary childcare provider and a support person at home (including at nighttime) while the patient is participating in the trial.	Oral doses of the IP should be taken within ±15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado), and with 240 mL (8 oz) of water. **For the IV bolus, ganaxolone 12 mg in 24 mL will be administered over 2 minutes via an indwelling catheter, or a butterfly, inserted in a vein on the arm or hand. The IP should be given as continuous infusion as instructed. The catheter should be flushed with saline at the end of the bolus infusion. For details please see pharmacy manual.** The **subject** must have a reliable family member, significant other or a trusted friend who can take the role for being the primary childcare provider and a support person at home (including at nighttime) while the **subject** is participating in the trial, **including for subjects who may stay overnight on the unit as part of the screening process and/or the PK subgroup.**
Reason for Change: Addition of information for IV ganaxolone administration and clarification of subjects who require support during the trial			

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
51	7 – Study Procedures	For the open-label safety group approximately 48 women 18 to 48 years of age with PPD will be screened to enroll approximately 24 patients. During this open-label safety phase, for the first approximately 8 subjects, ganaxolone will be titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days. This dosing group is called OL TID group. For the next approximately 8 subjects, ganaxolone will be administered at bedtime (QHS). For these subjects ganaxolone will be titrated to a QHS dose of 675 mg over 4 days which is then maintained until day 10, followed by a taper over 4 days. This dosing group is called OL QHS group. For the next approximately 8 subjects, ganaxolone will be administered at bedtime (QHS). For these subjects ganaxolone treatment will be a QHS dose of 675 mg over 28 days, followed by a taper over 4 days. This dosing group is called OL QHS 4-week group. The investigator has the flexibility to adjust the dose if the patient experiences sedation, dizziness or other untoward effects during the OL phase.	For the open-label safety part approximately **172** women 18 to 48 years of age with PPD will be screened to enroll approximately **88 subjects**. During this open-label safety part, for the first approximately 8 subjects, ganaxolone will be titrated to a daily dose of 900 mg/day over 10 days, followed by a taper over 4 days. This dosing group is called OL TID group. For the next approximately **20** subjects, ganaxolone will be administered at bedtime (QHS). For these subjects ganaxolone will be titrated to a QHS dose of 675 mg over 4 days which is then maintained until day 10, followed by a taper over 4 days. This dosing group is called OL QHS group. For the next approximately **20** subjects, ganaxolone will be administered at bedtime (QHS). For these subjects ganaxolone treatment will be a QHS dose of 675 mg over 28 days, followed by a taper over 4 days. This dosing group is called OL QHS 4-week group. **The next approximately 20 subjects of the open-label safety part will receive on the first 2 days ganaxolone capsules 675 mg at dinner time and 675 mg at bedtime (for a total of 1,350 mg per day on the first 2 days) followed by 26 days of ganaxolone capsules 1,125 mg at dinner time, followed by a taper over 4 days. This dosing group is called OL 1,125 mg group.** **For the next approximately 20 subjects of the open-label safety part, ganaxolone will be administered as IV bolus 12 mg over 2 minutes at approximately 4 pm on Day 1 followed by ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime, for a total of 1,512 mg on the first day. On Day 2 subjects will receive ganaxolone oral suspension 750 mg at dinner time and at 750 mg at bedtime, for a total of 1,500 mg, followed by 26 days of ganaxolone oral suspension 1000 mg at dinner time, followed by a taper over 4 days. This dosing group is called OL Bolus-Oral group. The investigator has the flexibility to adjust the dose and/or timing of the dose if the subject experiences sedation,**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		The open-label safety group will be enrolled, and dosing completed before proceeding to the double-blind group. The goal of the open-label group is to explore safety of oral ganaxolone in this population and identify a dosing regimen for the double-blind phase. For the double-blind group, approximately 100 women with PPD 18 to 48 years of age will be screened to randomize 50 women in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days. The dosing for the double-blind portion of the study will be decided based on the results of the open-label portion and recommendations of the DRC. The DRC is comprised of Marinus' Chief Medical Officer and 2 external physician experts. The daily dose will not exceed 1200 mg. Randomization will be stratified by the use of concomitant antidepressants so that the number of patients who are treated with antidepressants and who are not treated with antidepressants will be similar in each treatment group.	**dizziness or other untoward effects during the OL part (see Section 6.2.7).** The open-label safety **part** will be enrolled, and dosing completed before proceeding to the double-blind **part**. The goal of the open-label part is to explore safety of **IV and** oral ganaxolone in this population and identify a dosing regimen for the double-blind **part**. For the double-blind **part**, approximately 100 women with PPD 18 to 48 years of age will be screened to randomize 50 women in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days. The dosing for the double-blind portion of the study will be decided based on the results of the open-label portion and recommendations of the DRC. The DRC is comprised of Marinus' Chief Medical Officer and 2 external physician experts. The daily dose will not exceed **1,600 mg**. Randomization will be stratified by the use of concomitant antidepressants so that the number of **subjects** who are treated with antidepressants and who are not treated with antidepressants will be similar in each treatment group.
Reason for Change: Update to the number of subjects in each treatment group and maximum daily dose, and addition of 2 new treatment groups			
51	7 – Study Procedures	• Collect urine drug screen and urine pregnancy test	• Collect urine **for urinalysis, urine** drug screen and urine pregnancy test
Reason for Change: Clarification of urinalysis procedure			

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60	7.7 – Screening Period (Day -14 to -1) for OL 1,125 mg and OL Bolus-oral Groups		**7.7 Screening Period (Day -14 to -1) for OL 1,125 mg and OL Bolus-oral Groups** **7.7.1 Screening Visit (Visit 1)** • **Obtain written informed consent** • **Collect demographics, medical history, review prior medications, review of concomitant medications and therapies,** • **Assess CGI-S** • **Conduct Mini International Neuropsychiatric Interview 7.0 (MINI 7.0)** • **Conduct HAMD17 interview (if a HAMD17 interview was conducted for Marinus PPD study 1042-PPD-2002 at the same investigative site within 2 weeks of the screening visit the screening HAMD17 interview does not have to be repeated).** • **Perform EPDS** • **Perform STAI6** • **Perform a physical examination** • **Collect vital signs (blood pressure [BP], pulse, temperature, respiratory rate [RR])** • **Collect ECG** • **Collect urine for urinalysis, urine drug screen and urine pregnancy test** • **Collect safety laboratory tests** • **Measure height and weight** • **Conduct CSSRS interview** • **Review inclusion and exclusion criteria. Screen failure is defined as a subject who has given informed consent, and failed to meet the inclusion criteria and/or met the exclusion criteria** • **Schedule a SAFER interview if the subject meets the eligibility criteria. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study (if a SAFER interview was conducted within 2 weeks for Marinus PPD study 1042-**

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			PPD-2002 at the same investigative site the SAFER interview does not have to be repeated. In this instance the HAMD17 score from the SAFER interview can be used to qualify the subject for the study). • **Screening period may be extended to 21 days with approval from the medical monitor (e.g., a laboratory sample was hemolyzed and had to be repeated causing a delay).**
Reason for Change: Addition of screening period information for new treatment groups			
60	7.8 – Treatment Period (Day 1 to Day 29; Visits 2 to 7) for OL 1,125 mg and OL Bolus-oral Groups		**7.8 Treatment Period (Day ! to Day 29; Visits 2 to 7) for OL 1,125 mg and OL Bolus-oral Groups)** **7.8.1 Start of the Open-label Safety Period (Enrollment Visit for the OL 1,125 mg and OL Bolus-oral Groups) (Day 1)** • **The subject arrives in the clinic to complete baseline assessments on Day 1.** • **CTNI to conduct HAMD17 interview** • **Perform EPDS** • **Perform STAI6** • **Assess CGI-S** • **Review concomitant medications and therapies** • **Collect vital signs (BP, pulse, temperature, RR)** • **Measure weight** • **Collect ECG** • **Collect urine for urinalysis, urine drug screen and urine pregnancy test** • **Collect safety laboratory tests** • **Collect neurosteroid level** • **Collect SSS** • **Collect AEs** • **Conduct CSSRS interview** • **Review inclusion and exclusion criteria (including hematology, chemistry, urinalysis, urine drug screen and pregnancy tests from the screening visit); HAMD17 (as determined by CTNI) must be ≥ 18 for enrollment.** • **If the subject continues to meet the inclusion criteria**

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			and has not developed any exclusion criteria the subject will be enrolled in the study • **Dispense medication bottle after enrollment. Provide the subject with dosing instructions and subject diary completion.** • **For the OL 1,125 mg group: the subject will be instructed to take the first oral doses of the study medication that evening (675 mg [3 capsules] at dinner time [at 7 pm] and at bedtime [at 10 pm])** • **For the OL Bolus-Oral group: the subject will receive IV bolus 12 mg over 2 minutes at approximately 4 pm (preferably ±1 hour) while on the unit, be observed for development of sedation and/or other untoward effects for at least 1 hour post-bolus and then be discharged and instructed to take the first oral doses of the study medication that evening (750 mg [15 mL oral suspension at 50 mg per mL] at dinner time [at 7 pm] and at bedtime [at 10 pm])** • **Oral IP should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado), and with 240 mL (8 oz) of water.** • **A sub-group of 6 subjects (to be called 'PK sub-group', Section 7.10.7) in each of the OL 1,125 mg and OL Bolus-Oral groups will stay overnight on the unit between Day 1 and Day 2 to undergo comprehensive PK assessment as follows: for the OL 1,125 mg group plasma samples for PK analysis will be drawn at the following times after the first oral dose on Day 1 (i.e., the 675 mg oral capsules dose at 7 pm at dinner time; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the 10 pm 675 mg dose), at +4hr, +5hr, +6hr, and at 8 am on Day 2. For the OL Bolus-Oral group plasma samples for PK analyses will be drawn at the following times after the IV bolus on Day 1 (e.g., the 12 mg IV bolus at 4 pm; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the first oral dose of 750 mg oral suspension at dinner time), at +4hr, +5hr, +6hr (i.e., just prior to the second 750 mg oral suspension evening dose), at + 7hr, +8hr, and at 8 am on**

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			Day 2. • **If the subject is breastfeeding, she is encouraged to "pump and dump" during the study period and for 45 days after the last dose. She should be provided with a breast pump if she does not have one. Breast feeding is prohibited during the treatment phase and until 45 days following the last dose of the study drug.** **7.8.2 Treatment Visits (Days 2, 8, 15, 22, 29 ± 3 days [except Day 2]) for OL 1,125 mg and OL Bolus-oral Groups** • **CTNI to conduct interview for HAMD17** • **Conduct interview for CGI-I** • **EPDS** • **STAI6** • **Collect AEs** • **Collect ECG (Day 2, Day 8, Day 15, Day 29)** • **Collect vital signs (BP, pulse, RR, temperature)** • **Measure weight (Day 15, Day 29)** • **Collect SSS** • **Collect a PK sample** • **Record concomitant medications** • **Collect safety laboratory tests (Day 15, Day 29)** • **Collect neurosteroid level (Day 2, Day 8, Day 15, Day 29)** • **Collect urine for urinalysis, urine drug screen and urine pregnancy test (Day 8, Day 15, Day 22, Day 29)** • **Conduct CSSRS interview** • **Perform a physical examination (Day 29)** • **Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions.** • **For the OL 1,125 mg group: the subject will be instructed to take Day 2 oral doses of the study medication that evening (675 mg [3 capsules] at dinner time [at 7 pm] and 675 mg [3 capsules] at bedtime [at 10 pm]) followed by 26 days of 1,125 mg (5 capsules) at dinner time**

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			• **For the OL Bolus-Oral group: the subject will be instructed to take Day 2 oral doses of the study medication that evening (750 mg [15 mL oral suspension at 50 mg per mL] at dinner time [at 7 pm] and 750 mg [15 mL oral suspension at 50 mg per mL] at bedtime [at 10 pm]) followed by 26 days of 1,000 mg (20 mL oral suspension at 50 mg per mL) at dinner time** • **Oral IP should be taken within ±15 minutes of a fatty meal or snack (e.g., yogurt, nuts, avocado), and with 240 mL (8 oz) of water.** • **During Visit 7 (Day 29) start study drug taper (Day 29-32) (See Sections 6.2.5 and 6.2.6)**
Reason for Change: Addition of treatment period information for new treatment groups			
63	**7.9 - Follow-up Visit 1 (Day 36 ± 3), Follow-up Visit 2 (Day 57 ± 3), and Follow-up Visit 3 (Day 71 ± 3) for the OL 1,125 mg and OL Bolus-Oral groups**		**7.9 – Follow-up Visit 1 (Day 36 ± 3), Follow-up Visit 2 (Day 57 ± 3), and Follow-up Visit 3 (Day 71 ± 3) for the OL 1,125 mg and OL Bolus-Oral Groups** • The Follow-up Visit 1 should occur about 1 week after D29 visit, and about 4 days after the subject has taken her last dose of the study medication. The Follow-up Visit 2 should occur approximately 21 days after Follow-up Visit 1. The Follow-up Visit 3 should occur approximately 14 days after Follow-up Visit 2 (All Follow-up visits should be scheduled within visit window unless there is a medical need to see the subject sooner; an additional safety visit can be scheduled as per the investigator's discretion). • CTNI to conduct interview for HAMD17 • Conduct interview for CGI-I • Perform EPDS • Perform STAI6 • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, RR) • ECG (Follow-up Visit 1 only) • Collect safety laboratory tests (Follow-up Visit 1 and 3 only) • Collect neurosteroid level (Follow-up Visit 1 and 3 only) • Collect PK sample (Follow-up Visit 1 only) • Collect urine for urinalysis, urine drug screen and urine

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pregnancy test
- Measure weight (Follow-up Visit 3 only)
- Conduct CSSRS interview
- Collect SSS
- Collect AEs
- Collect study medication bottle dispensed at Day 29 (Follow-up Visit 1 only). Review subject dosing diary and complete drug accountability while subject is present.

Table 8. Schedule of Assessments for the Open-label OL 1,125 mg and OL Bolusoral Groups

VISIT	**Screening (V1)**	**Day 1 (V2)**	**Day 2 (V3)**	**Day 8 ±3d (V4)**	**D15 ±3d (V5)**	**Day 22 ±3d (V6)**	**Day 29 ±3d (V7)**	**Day36 ±3d (V8; 1st FU)**	**Day 57 ±3d (V9; 2nd FU)**	**Day71 ±3d (V10; 3rd FU)**
Informed	X									
Demographics,	X									
MINI	X									
Inclusion/Exclu	X	X								
Dispense medication /		X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Physical	X						X			
SAFER	X									
Vital signs	X	X	X	X	X	X	X	X	X	X
Height	X	X			X		X			X
ECGs	X	X	X	X	X		X	X		
Safety	X	X			X		X	X		X
[b] Bolus **(OL**		X								
PK sample			X	X	X	X	X	X		
PK subgroup sample collection		[c] X								

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Neurosteroid		X	X	X	X		X	X		X
Urinalysis,	X	X		X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X	X	X
[a] HAMD17	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
CGI-S	X	X								
EPDS	X	X	X	X	X	X	X	X	X	X
STAI6	X	X	X	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X	X	X	X
SSS		X	X	X	X	X	X	X	X	X
Start Taper							X			

[a] CTNI will conduct all HAMD ratings except the one at screening

[b] IV bolus is to be done at approximately 4 pm (preferably within ±1 hour) and allowing for at least 1-hour post-bolus follow-up at the site before discharge

[c] A sub-group of 6 subjects (to be called 'PK sub-group') in each of the OL 1,125 mg and OL Bolus-Oral groups will stay overnight on the unit between Day 1 and Day 2 to undergo comprehensive PK assessment as follows: for the OL 1,125 mg group plasma samples for PK analysis will be drawn at the following times after the first oral dose on Day 1 (e.g., the 675 mg oral capsules dose at 7 pm at dinner time; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the 10 pm 675 mg dose), at +4hr, +5hr, +6hr, and at 8 am on Day 2. For the OL Bolus-Oral group plasma samples for PK analyses will be drawn at the following times after the IV bolus on Day 1 (e.g., the 12 mg IV bolus at 4 pm; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the first oral dose of 750 mg oral suspension at dinner time), at +4hr, +5hr, +6hr (i.e., just prior to the second 750 mg oral suspension evening dose), at + 7hr, +8hr, and at 8 am on Day 2.

The following priority order will be in effect when more than 1 assessment is required at a particular time point: 1) HAMD17 2) CGI-I/CGI-S 3) EPDS 4) STAI6 5) SSS 6) CSSRS 7) vital signs 8) ECG 9) safety labs 10) neurosteroid sample 11) PK sample 12) urinalysis, urine drug screen and pregnancy test 13) physical examination. SAFER interview is scheduled if subject meets the eligibility criteria at the Screening visit. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study. Screening period may be extended to 21 days with approval from the medical monitor.

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
Reason for Change: Addition of follow-up period information for new treatment groups			
66	7.10.4 – Prior Medication, Concomitant Medication and Concomitant Therapy Review	At screening, prospective subjects will be asked about medications they have taken in the previous 60 days, including prescription medications, non-prescription medications, vitamins, and supplements. At subsequent visits, the subjects will be asked about mediations taken since the last visit. The type of psychological counseling the subject is receiving at the time of screening will be recorded on the Concomitant Psychological Treatment eCRF page.	At screening, prospective subjects will be asked about medications they have taken in the previous 60 days, including prescription medications, non-prescription medications, **herbal medications,** vitamins, and supplements. At subsequent visits, the subjects will be asked about medications taken since the last visit. The type of psychological counseling the subject **received from** the time of screening **through the last follow-up visit** will be recorded on the Concomitant Psychological Treatment eCRF page.
Reason for Change: Clarification of concomitant medications and time period for follow-up			
66	7.10.5 - Physical Examination	A complete physical examination will be performed at screening and at Day 10 visit (Day 29 for OL QHS 4 week group).	A complete physical examination will be performed at screening and at Day 10 visit (Day 29 for OL QHS 4 week, **OL 1,125 mg and OL Bolus-Oral groups**).
Reason for Change: Addition of 2 new treatment groups			
70	7.10.6.7 – SAFER Interview		**CTNI will also perform all HAMD ratings except the one done at screening.**
Reason for Change: Clarification of SAFER interview for study			
70	7.10.7 – Pharmacokinetic Sampling		**A sub-group of 6 subjects (to be called 'PK sub-group') in each of the OL 1,125 mg and OL Bolus-Oral groups will stay overnight on the unit between Day 1 and Day 2 to undergo comprehensive PK assessment as follows: for the OL 1,125 mg group plasma samples for PK analysis will be drawn at the following times after the first oral dose on Day 1 (i.e., the 675 mg oral capsules dose at 7 pm at dinner time; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the 10 pm 675 mg dose), at +4hr, +5hr, +6hr, and at 8 am on Day 2. For the OL Bolus-Oral group plasma samples for PK analyses will be drawn at the following times after the IV bolus on Day 1 (e.g., the 12 mg IV bolus at 4 pm; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the first oral dose of 750 mg oral suspension at dinner time), at +4hr, +5hr, +6hr (i.e., just prior to the second 750 mg oral suspension evening dose), at + 7hr, +8hr, and at 8 am on Day 2.**

<table>
<tr><th>Page</th><th>Section, Title, Paragraph, Line</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td></td><td></td><td>The first 6 consecutively enrolled subjects who are in units with overnight inpatient capabilities and who consent for inclusion in the PK subgroup will be included in the PK subgroup.</td></tr>
<tr><td colspan="4">Reason for Change: Addition of PK sub-group from the additional treatment groups</td></tr>
<tr><td>71</td><td>7.10.9 – Volume of Blood to be Drawn from Each Subject</td><td>Table 7. Volume of Blood to Be Drawn from Each Subject for the OL QHS 4 Week</td><td>Table 10. Volume of Blood to Be Drawn from Each Subject for the OL QHS 4 Week, OL 1,125 mg, and OL Bolus-Oral groups

Table 11. Volume of Blood to be Drawn from Each Subject for the PK Subgroup of OL 1,125 mg Group
<table>
<tr><th>Assessment</th><th>Approximate Sample Volume (mL)[a]</th><th>Number of Samples</th><th>Approximate Total Volume (mL)</th></tr>
<tr><td>Pharmacokinetic samples</td><td>4</td><td>12</td><td>48</td></tr>
<tr><td>Safety hematology</td><td>3</td><td>6</td><td>18</td></tr>
<tr><td>Safety chemistry</td><td>7</td><td>6</td><td>42</td></tr>
<tr><td>Neurosteroid level</td><td>4</td><td>7</td><td>28</td></tr>
<tr><td>Total mL</td><td></td><td></td><td>136</td></tr>
</table>
Table 12. Volume of Blood to be Drawn from Each Subject for the PK Subgroup of OL Bolus-oral Group
<table>
<tr><th>Assessment</th><th>Approximate Sample Volume (mL)[a]</th><th>Number of Samples</th><th>Approximate Total Volume (mL)</th></tr>
<tr><td>Pharmacokinetic samples</td><td>4</td><td>14</td><td>56</td></tr>
</table></td></tr>
</table>

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		During this study, approximately 58 mL of blood will be drawn from all subjects during the study for the OL TID,OL QHS and Double-blind groups. Approximately 112 mL of blood will be drawn from all subjects during the study for the OL QHS 4 week group.	Safety hematology 3 6 18 Safety chemistry 7 6 42 Neurosteroid level 4 7 28 Total mL 144 During this study, approximately 58 mL of blood will be drawn from all subjects during the study for the OL TID, OL QHS and Double-blind groups. Approximately 112 mL of blood will be drawn from all subjects during the study for the OL QHS 4 week, **OL 1,125 mg, and OL Bolus-Oral groups.** **Subjects in the 'PK subgroup' of the OL 1,125 mg and OL Bolus-Oral groups (6 subjects in each subgroup) will have additional 6 and 8 samples, respectively, at 4 mL each, for a total of approximately 136 mL and 144 mL of blood drawn, respectively.**
Reason for Change: Addition of 2 treatment groups			

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
78	9.3 - Statistical Analysis Plan	The SAP will be finalized prior to completion of the double-blind phase to preserve the integrity of the statistical analysis and study conclusions.	The SAP will be finalized prior to **database lock and/or unblinding of any portion of the trial to** preserve the integrity of the statistical analysis and study conclusions.
Reason for Change: Clarification of SAP finalization			
78	9.3.1 – Data Review Committee (DRC) and Recommendations for Dosing	Marinus may decide to stop the study, or make the data public, after completion of the open-label group or the double-blind phase of the study.	Marinus may decide to stop the study, or make the data **public at any time during the open-label portion of the trial or** after completion of the double-blind **part** of the study.
Reason for Change: Clarification of study stopping procedures			
79	9.3.2 – Justification for Sample Size	A sample size of 20 patients per group would be needed to detect a 3.5 point difference on the HAMD17 scale assuming standard deviation of 3.5 with power=86%, alpha=0.05, and 2-sided t-test. A sample size of 20 patients per group would be needed to detect a 5 point difference on the HAMD17 scale assuming standard deviation of 3.5 with power=99%, alpha=0.05, and 2-sided t-test. In a recent study by Hantsoo et al., (2014) sertraline was shown to be effective in treatment of PPD over 6 weeks of treatment (n=27; subset of women with strictly defined PPD). The separation between sertraline and placebo was 7.8 points at the study end-point. Standard deviations were 2.8 and 3.9 for the placebo and sertraline groups, respectively.	**With a sample size of 50 subjects/group, the DBPC part of the trial will be able to detect a medium effect size (per Cohen's d) with 93% power using a two-sided significance level of 0.05.**
Reason for Change: Clarification of justification for sample size			
79	9.3.3 – Study Population	The **modified Intent to Treat Set** (mITT) will consist of all subjects in the Safety Set who have at least 1 post-enrollment HAMD17 assessment. The mITT set will be used for all efficacy assessments.	The **Randomized Set** will consist of subjects randomized in the DBPC part of the trial. The **modified Intent to Treat Set** (mITT) will consist of all subjects in the **DBPC part of the trial who received IP and** who have at least 1 **post-baseline** HAMD17 assessment. The mITT set will be **the primary efficacy population for the DBPC part of the trial.**
Reason for Change: Addition of definition of randomized set and clarification of mITT set			

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
79	9.4 – Analysis Methods		Data will be presented by study part (OL, DBPC), dosing or treatment group within study part and, if applicable, study visit. Continuous variables will be summarized as numbers of observations, means, measures of variance (e.g., standard deviation), and percentiles (e.g., median, minimum, maximum). Categorical variables will be summarized as numbers of observations and percentages.
Reason for Change: Addition of analysis methods			
79	9.4.1 – Demographic and Baseline Characteristics	Descriptive summaries of demographic and baseline characteristics as well as subject disposition will be presented by study phase (open-label safety group, double-blind phase) and by treatment within the double-blind phase. Baseline characteristics will include a summary of the following: • Subject demographics • Pre-existing medical conditions • Prior therapies. Continuous variables such as age, weight, and height will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables, like sex and race, will be summarized using number of observations and percentages. Medical history will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.	Baseline characteristics will include a summary of the following: • Subject demographics • Pre-existing medical conditions • Prior therapies • Medical history
Reason for Change: Clarification of analysis method			
80	9.4.2 – Subject Disposition		**Frequencies and percentages of subjects who discontinued the study and reasons for discontinuation will be summarized.**
Reason for Change: Clarification of analysis method			
80	9.4.3 – Investigational Medicinal Product	Summary statistics for the duration of exposure to investigational medicinal product, will be presented by study phase and by treatment group.	**Overall exposure to IP, such as** duration of exposure, **as well as dose adjustments (i.e, deviations from the scheduled titration scheme)** will be **summarized.**
Reason for Change: Clarification of analysis method			

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
80	9.4.4 – Concomitant Medication	Concomitant medications will be listed and summarized by preferred drug name by study phase and treatment group.	Concomitant medications will be **coded using the World Health Organization Drug Dictionary (WHO-DD)** and **will be** summarized by **drug class and** preferred drug name.
Reason for Change: Clarification of analysis method			
80	9.4.5 – Safety Analyses	Reported AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of Treatment Emergent AEs (TEAEs) will be summarized by treatment group, system organ class preferred terms, severity and relatedness for the open-label safety group and double-blind phase. SAEs and AEs leading to discontinuation of the study drug will be summarized by study phase (open-label safety group and double-blind phase) and treatment group. The absolute values and change from baseline in laboratory tests, vital signs, SSS, ECGs, and CSSRS will be summarized by study phase (open-label safety group and double-blind phase) and treatment group. Dose adjustments (i.e, deviations from the scheduled titration scheme) will be summarized. Potentially clinically important findings will be summarized or listed. Results of the physical examination will be listed.	Reported AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment emergent AEs (TEAEs), **defined as AEs that started or worsened after first administration of IP,** will be summarized by system organ class **and** preferred term. **Separate summaries of TEAEs by** severity and relatedness **will be done**. SAEs and **TEAEs** leading to discontinuation of the study drug will **also** be summarized **separately.** The absolute values and change from baseline in laboratory tests, vital signs, SSS, **ECG parameters**, and CSSRS will be summarized. Results of physical examinations will be listed.
Reason for Change: Clarification of safety analyses			
80	9.4.6 – Efficacy Analyses	Approximately continuous endpoints (e.g, HAMD17, HAMD6, STAI6, and EPDS) will be analyzed by mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) including all post-baseline treatment visits (but not the follow-up visits). The model will include fixed effects of treatment, visit, treatment-by-visit interaction, and baseline value of the endpoint. If at least 8 subjects are taking concomitant antidepressants during the study, it will also be included as a fixed effect. An unstructured residual covariance matrix will be used; however alternate structures,	**Efficacy parameters will be summarized for both the OL and DBPC parts but will be analyzed only for the DBPC part. For the OL part, referring to efficacy endpoints as "primary," "secondary," and "exploratory" is related to the degree of influence each type of endpoint is expected to have on decision-making rather than to considerations associated with inferential analysis (such as control of type 1 error). The primary time point of interest for all efficacy parameters will be Day 10 for the DBPC part and the visit at**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
		to be specified in the SAP, will be used in the event of convergence issues. Differences between the treatments overall and at each visit will be tested for statistical significance. Ordered categorical endpoints (CGI-I, EPDS obsessive thoughts - time occupied, EPDS obsessive thoughts – distress) will be analyzed at each visit by the Cochran-Mantel-Haenszel (CMH) row mean scores test using rank scores. Dichotomous categorical endpoints will be analyzed at each visit by Fisher's exact test [HAMD17 response (≥ 50% decrease from Baseline), HAMD6 response (≥ 50% decrease from Baseline), HAMD17 remission (HAMD17 total score ≤ 7]. However, if concomitant antidepressants are included in the model of approximately continuous endpoints, then the CMH row means scores test will control for their use, and the Fisher's exact test will be replaced with the CMH general association test, controlling for their use. Items related to sleep and anxiety within the HAMD17 and EPDS scales may be tabulated separately. After the completion of the double-blind phase and analysis of the data by the DRC Marinus may decide to enroll another group of subjects who are randomized to receive ganaxolone or placebo. Since this is a Phase 2 study, no adjustments to the Type I error protections are considered necessary. Efficacy data for the open-label safety group will be summarized descriptively.	**end of treatment (before initiation of taper) for the OL part.**
Reason for Change: Clarification of efficacy analyses			
80	9.4.6.1 – Primary Endpoint		**The primary efficacy endpoint will be HAMD17 total score change from baseline; this will be assessed at Day 10 for the DBPC part and at the visit at end of treatment for the OL part. The primary efficacy analysis will be done using the mITT set (DBPC part only). The analytical method will be mixed model repeated measures (MMRM) with baseline HAMD17 total score as a covariate. Significance will be**

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			tested at a two-sided 0.05 level. Unstructured covariance will be specified although alternative covariance structures may be used, if appropriate, to achieve convergence or greater efficiency. Sensitivity analysis will be used to evaluate the assumption of data missing at random (MAR), if applicable.
Reason for Change: Addition of analysis method			
81	9.4.6.2 – Secondary Endpoints		**The trial will also evaluate the following secondary endpoints at each post-baseline data collection time point to provide additional evidence of the efficacy of ganaxolone in treating PPD:** **• Change from baseline in HAMD17 total score other than at the primary endpoint time point** **• HAMD17 response defined as at least a 50% reduction from baseline in total score** **• HAMD17 remission defined as total score <= 7** **• Change from baseline in EPDS total score** **• Change from baseline in STAI6** **• CGI-I**
Reason for Change: Addition of analysis method			
81	9.4.6.3 – Exploratory Endpoints		**Several endpoints will be evaluated for signals of efficacy to explore whether any should be elevated in importance in subsequent trials. Change from baseline to each post-baseline data collection time point will be summarized for the following exploratory endpoints:** **• HAMD6 (Bech) subscale of HAMD17: depressed mood, feelings of guilt, work and activities, retardation, anxiety psychic, and general somatic symptoms (Items 1, 2, 7, 8, 10, 13)** **• Anxiety/Somatization subscale of HAMD17: anxiety psychic, anxiety somatic, somatic symptoms gastro-intestinal, general somatic symptoms, hypochondriasis, and insight (Items 10-13, 15, 17)** **• Gibbons Global Depression Severity subscale of HAMD17: depressed mood, feelings of guilt, suicide, work and activities, agitation, anxiety psychic, anxiety somatic,**

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
			genital symptoms (Items 1-3, 7, 9-11, 14) • **HAMD17 individual items** • **Anxiety subscale derived from EPDS Items 3-5 ("I have blamed myself unnecessarily when things went wrong," "I have been anxious or worried for no good reason," "I have felt scared or panicky for no very good reason")** • **EPDS individual items**
Reason for Change: Addition of analysis method			
81	9.4.6.4 – Statistical Methods		**Efficacy parameters will be summarized for OL and DBPC parts. Observed values and changes from baseline for HAMD17, EPDS, and STAI6 total scores, subscales, and individual items will be summarized by visit. The categorical outcomes of HAMD17 response, HAMD17 remission, and CGI-I will be summarized by visit.** **For the DBPC part, the preferred approach for analyses of treatment group differences in secondary and exploratory continuous efficacy variables will be MMRM but other approaches such as t-tests, analysis of covariance, or non-parametric methods may be used if necessary or more practical. Similarly, the preferred approach for analysis of secondary and exploratory categorical efficacy variables will be repeated measures (e.g., generalized estimating equations) but other approaches such as chi square or Fisher's exact tests may be used.**
Reason for Change: Addition of statistical methods for each part of the study			